

How I Manage Chronic Lymphocytic Leukemia

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Introduction

The therapeutic landscape for chronic lymphocytic leukemia (CLL) has changed dramatically in the last several years.¹ The role of chemoimmunotherapy has declined, and we are increasingly using targeted therapies. This overview focuses on frontline therapy for CLL and includes a case-based discussion.

Initial Evaluation of the Patient With Newly Diagnosed CLL

For patients presenting with early-stage CLL (Rai stage 0, or Rai stage 1-2 with small-volume adenopathy/organomegaly), we typically perform peripheral blood flow cytometry to confirm the diagnosis of CLL. In our practice, we obtain a CLL fluorescence in situ hybridization (FISH) panel to detect chromosomal aberrations and also obtain information on prognostic markers, such as the *IGHV* mutation status and *TP53* mutation status. Knowing the status of these genes helps in assessing the expected time to first treatment because early progression is more likely in patients with unmutated *IGHV* and those with a *TP53* aberration. One can also defer assessment of the prognostic marker status until the time when disease progression necessitates first-line therapy. It is important to note that the *IGHV* mutation status of an individual patient does not change over time and therefore needs to be determined only once. The CLL FISH panel and *TP53* mutation testing should be repeated before each therapy, as these can evolve over time (clonal evolution, such as with the acquisition of del(17p) or a *TP53* mutation in patients receiving chemoimmunotherapy). We do not routinely have patients with newly diagnosed CLL undergo computed tomography (CT) unless significant intra-abdominal adenopathy is a concern or the patient is deemed to require treatment. We have patients with suspected Richter transformation, such as those with rapidly progressive adenopathy, significant B symptoms,

or elevated lactate dehydrogenase, undergo positron emission tomography; the goal is to perform a biopsy of the site with the highest standardized uptake value (SUV). An SUV of 7 or higher is relatively infrequent in CLL and is suggestive of Richter transformation or other conditions, such as infection.²⁻⁵

Once early-stage CLL has been diagnosed and we have determined that therapy is not indicated, patients are monitored with a complete blood cell count and physical examination every 3 to 6 months. At each visit, patients should be evaluated to see if the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) treatment criteria have been met.⁶ Once it has been determined that a patient meets the treatment criteria, prognostic marker testing should be obtained if it has not been done previously. We also routinely obtain bone marrow and CT scans before initiating first-line therapy. CT scans are especially important if venetoclax-based therapy is planned, so that the patient's tumor lysis syndrome risk can be categorized accurately.

Patient Cases

Case No. 1

The first patient is a 64-year-old man in whom CLL was recently diagnosed after he presented with an elevated white blood cell (WBC) count. He is asymptomatic from the standpoint of the disease. On examination, he has no palpable lymph nodes. His WBC count is 25,000/ μ L with 80% lymphocytes, his hemoglobin level is 13.4 g/dL, and his platelet count is 235,000/ μ L. Peripheral blood flow cytometry confirms the diagnosis of CLL. Testing for prognostic markers in the peripheral blood detects unmutated *IGHV*, and FISH analysis indicates the presence of del(17p). What is the appropriate next step in the management of this patient?

Discussion. This patient has newly diagnosed Rai stage 0 CLL. He is asymptomatic, and the only evidence of disease is lymphocytosis. No palpable adenopathy or cytopenias are present. He does not meet the criteria

for treatment per the iwCLL guidelines. He does have del(17p), which puts him at high risk because disease tends to progress earlier in patients with this aberration. At present, several ongoing trials are evaluating targeted therapies, such as Bruton tyrosine kinase (BTK) inhibitors and therapies based on venetoclax (Venclexta, AbbVie), for patients with high-risk early-stage CLL.^{7,8} Until we have favorable long-term follow-up data from these trials, however, the standard recommendation for patients with early-stage CLL remains active surveillance, even if they have high-risk features. Patients should not be treated for CLL until they meet the iwCLL treatment criteria.

Case No. 2

The second patient is 56-year-old woman in whom CLL was diagnosed 5 years ago. At that time, she was advised to undergo clinical observation. Over the course of the last 5 years, she has experienced gradual progression of her CLL, with the development of progressive adenopathy, lymphocytosis, anemia, and thrombocytopenia. She is reporting worsening fatigue. On examination, lymph nodes measuring 3 to 4 cm are palpable bilaterally in the cervical and axillary areas. Her WBC count is 135,000/ μ L with 90% lymphocytes, her hemoglobin level is 9.5 g/dL, and her platelet count is 82,000/ μ L. Testing for prognostic markers reveals mutated *IGHV*, and FISH analysis indicates the presence of del(13q). A *TP53* mutation is not detected. CT confirms progressive multicompartment adenopathy. The patient has no significant medical comorbidities. What is the appropriate next treatment?

Discussion. This patient is 56 years old and has no significant medical commodities. She clearly meets the iwCLL treatment criteria on the basis of the development of progressive adenopathy, anemia, and thrombocytopenia. Until recently, the standard therapy for younger patients with CLL was chemoimmunotherapy, such as 6 cycles of fludarabine, cyclophosphamide, and rituximab (FCR). The initial phase 2 study from the MD Anderson Cancer Center (MDACC) of the FCR regimen in patients with previously untreated CLL reported an overall response rate of 95%, with a complete remission (CR) rate of 72%.⁹ In a follow-up report, patients with mutated *IGHV* had a 10-year progression-free survival (PFS) rate of approximately 55% after receiving FCR in the first-line setting, with a plateau on the curve, indicating a potential for “cure” in this patient subgroup.¹⁰ Other groups have reported similar data with FCR for long-term PFS in patients with mutated *IGHV*.^{11,12} The German CLL Study Group conducted a randomized trial, called CLL10, of FCR vs bendamustine and rituximab (BR) in patients with previously untreated CLL.¹³ Compared with the BR arm, the FCR arm had a higher CR rate (39.7% vs 30.8%; $P=.03$) and a longer median PFS (57.6 vs 42.3

months; $P<.001$).^{13,14} As expected, the FCR regimen led to higher rates of myelosuppression and infections. The CLL10 trial established FCR as the standard first-line therapy for young, fit patients with CLL.

More recently, in the E1912 trial, patients with CLL were randomly assigned to receive FCR for 6 cycles or ibrutinib (Imbruvica, Pharmacylics/Janssen) and rituximab.¹⁵ Ibrutinib was given continuously daily and rituximab was given for 6 months. The 3-year PFS was 89% with ibrutinib plus rituximab vs 71% with FCR ($P<.0001$).¹⁶ In a subgroup analysis, the PFS benefit was restricted to patients with *IGHV*-unmutated CLL. Among the patients with *IGHV*-mutated CLL, the PFS curves were overlapping. Therefore, in our opinion, the treatment approach of FCR for 6 cycles in patients with mutated *IGHV* is reasonable, as is targeted therapy. Longer follow-up data from this trial are eagerly awaited, especially data for the *IGHV*-mutated subgroup. If using FCR chemoimmunotherapy, patients should be informed of the long-term risk for therapy-related myelodysplastic syndromes and acute myeloid leukemia. Given the multitude of targeted therapies available these days for patients with CLL, and the potential complications of chemoimmunotherapy, an increasing number of patients are receiving targeted therapies. In addition to ibrutinib, the BTK inhibitor acalabrutinib (Calquence, AstraZeneca) and a combination of venetoclax and obinutuzumab (Gazyva, Genentech) are approved as first-line therapy in CLL.^{17,18}

For this patient, outside a clinical trial setting, we would offer a choice among 4 therapies: (1) FCR chemoimmunotherapy, (2) ibrutinib, (3) acalabrutinib, or (4) a combination of venetoclax and obinutuzumab. FCR and venetoclax plus obinutuzumab are time-limited approaches, whereas the 2 BTK inhibitors (ibrutinib and acalabrutinib) are intended to be given daily indefinitely. All of these approaches have their advantages and disadvantages, which should be discussed with the patient before the treatment option is selected.

Case No. 3

The third patient is a 76-year-old man in whom CLL was diagnosed 1 year ago. At that time, the recommended management plan was clinical observation. The patient now has progressive disease with the development of cytopenias. He has worsening symptoms. His WBC count is 125,000/ μ L, his hemoglobin level is 9.2 g/dL, and his platelet count is 72,000/ μ L. The CLL FISH panel shows del(17p), *IGHV* is unmutated, and a *TP53* mutation is detected. What is the best treatment for the patient at this time?

Discussion. This patient has del(17p) and a *TP53* mutation, which are associated with resistance to chemotherapy. Before the introduction of targeted therapies,

Table 1. Rates of Measurable Residual Disease Across Selected Trials of First-Line Combination Treatments in CLL

Regimen (Trial)	Reference	N	U-MRD4 Rate (Cycle)	
			Peripheral Blood	Bone Marrow
Ven + G (CLL14)	Al-Sawaf, ASH 2020 ²⁸	216	76% (C12)	57% (C12)
Ibr + Ven (MDACC)	Jain, ASH 2020 ³⁰	80	-	56% (C12); 66% (C24)
Ibr + Ven (CAPTIVATE)	Wierda, ASH 2020 ³¹	164	75% (C12)	68% (C12)
Ibr + Ven + G	Rogers, ASH 2020 ³²	25	72% (C16)	60% (C16)
Ibr + Ven + G (CLL2-GIVE) <i>TP53</i> -aberrant only	Huber, EHA 2020 ³³	41	80% (C15)	68% (C15)
Aca + Ven + G	Davids, ASH 2020 ³⁴	44	84% (C16)*	76% (C16)*
Zan + Ven + G (BOVen)	Soumerai, ASH 2020 ³⁵	39	89% (C10)*	89% (C10)*

Note: Data are from the intention-to-treat group unless indicated with asterisk.

*Data are from evaluable patients.

Aca, acalabrutinib; ASH, American Society of Hematology; C10, response after cycle 10; EHA, European Hematology Association; G, obinutuzumab; Ibr, ibrutinib; Ven, venetoclax; U-MRD4, undetectable measurable residual disease on assay with sensitivity of 10⁻⁴; Zan, zanubrutinib.

patients with these characteristics were treated with chemotherapy and had a dismal PFS of approximately 12 months.^{19,20} Therefore, this patient should not receive chemotherapy. In the front-line setting, the available options for targeted therapy include ibrutinib, acalabrutinib, and a combination of venetoclax and obinutuzumab. Recently, a group from the National Institutes of Health (NIH) reported favorable long-term outcomes in 34 patients who had either del(17p) with or without *TP53* mutation (n=32) or a *TP53* mutation without del(17p) (n=2).²¹ Unmutated *IGHV* was noted in 62% of the patients. The 5-year PFS was noted to be favorable, at 70%, with a statistically significant difference found between the patients with mutated and those with unmutated *IGHV*. In a pooled analysis of 4 different clinical trials of ibrutinib (with or without a CD20 monoclonal antibody) as first-line therapy, Allan and colleagues reported outcomes in 89 patients.²² Approximately half of the patients received ibrutinib monotherapy; the remaining received ibrutinib with a CD20 monoclonal antibody. Unmutated *IGHV* was noted in 69% of the patients. The estimated 4-year PFS rate was 79%, similar to that seen in the NIH report. Acalabrutinib was studied in a phase 1/2 trial enrolling patients with previously untreated CLL.²³ This study included 12 patients with a *TP53* aberration. The estimated 4-year PFS rate was 82%.

The responses to time-limited 1-year treatment with venetoclax plus obinutuzumab have not been durable in *TP53*-aberrant patients. In the CLL14 trial, 25 patients with a *TP53* aberration received venetoclax plus obinutuzumab.²⁴ Disease relapse continued after they had stopped venetoclax at 1 year per protocol, and the estimated 3-year PFS rate was only 60%.

For this patient, therapy with a BTK inhibitor is preferred. BTK inhibition with either ibrutinib or acalabrutinib is appropriate. Enrollment in clinical trials exploring combination targeted therapies should be encouraged.

Case No. 4

The fourth patient is a 72-year-old woman in whom CLL was diagnosed 2 years ago. She now has worsening symptoms with progressive adenopathy. She presents for consideration of therapy options. Prognostic markers include unmutated *IGHV* and the presence of del(11q) by FISH analysis. A *TP53* mutation is not detected. She has no major comorbidities, and her renal function is normal. What is the appropriate therapy for this patient?

Discussion. This patient meets the iwCLL treatment criteria. She has unmutated *IGHV* and the presence of del(11q). Long-term PFS is not achieved with chemoimmunotherapy in patients who have unmutated *IGHV*. In the Alliance trial comparing BR vs ibrutinib vs ibrutinib and rituximab, the PFS was longer in the 2 ibrutinib arms than in the BR arm.²⁵ This benefit was seen largely among patients with unmutated *IGHV*. Given this finding, treatment with an approach not based on chemotherapy is a preferred strategy for this patient. Currently, approved options for first-line targeted therapy in CLL include ibrutinib, acalabrutinib, and the combination of venetoclax plus obinutuzumab. These strategies have their pros and cons, which should be considered before a therapy option is chosen. Ibrutinib was the first BTK inhibitor approved and has the longest track record.^{26,27} However, ibrutinib is associated with a risk for atrial fibrillation and an increase in bleeding complications. Acalabrutinib is a second-generation BTK inhibitor

Table 2. Selected Phase 3 Trials of First-Line Treatment in CLL

Trial	N	Randomization			
		Control Arms	Investigational Arms		
UK FLAIR	1576	FCR	Ibr + R	Ibr	Ven + Ibr
CLL13	920	FCR/BR	Ven + G	Ven + R	Ven + Ibr + G
ACE-CL-311	780	FCR/BR	Aca + Ven	Aca + Ven + G	
CRISTALLO	165	FCR/BR	Ven + G		
SEQUOIA	450	BR	Zan		
GLOW	200	Clb + G	Ven + Ibr		
EA9161	720	Ibr + G	Ibr + G + Ven		
A041702	454	Ibr + G	Ibr + G + Ven		
CLL17	897	Ibr	Ven + G	Ven + Ibr	

Aca, acalabrutinib; BR, bendamustine and rituximab; Clb, chlorambucil; FCR, fludarabine, cyclophosphamide, and rituximab; G, obinutuzumab; Ibr, ibrutinib; R, rituximab; Ven, venetoclax; Zan, zanubrutinib.

with less off-target kinase inhibition than ibrutinib.¹⁷ It appears to have an improved safety profile compared with ibrutinib; the results of a head-to-head comparison of acalabrutinib vs ibrutinib in relapsed or refractory CLL (the ELEVATE RR trial; NCT02477696) are awaited. The recommendation that both ibrutinib and acalabrutinib be given indefinitely adds to the cost of the treatment. The combination of venetoclax plus obinutuzumab was investigated in a phase 3 randomized trial comparing this regimen with the combination of chlorambucil and obinutuzumab (the CLL14 trial).¹⁸ Obinutuzumab was given for 6 months and venetoclax for a total of 1 year. All patients stopped therapy at 1 year, irrespective of their response. The estimated 4-year PFS rate with the combination of venetoclax and obinutuzumab was recently reported at 76%.²⁸ This strategy leads to higher rates of CR as well as of undetectable measurable residual disease (U-MRD) in both peripheral blood and bone marrow. Patients need to be monitored closely for tumor lysis syndrome. Grade 3 or 4 neutropenia is seen in approximately 50% of patients.

The 3 strategies described above should be discussed with this patient, including the pros and cons of each therapy. For patients with renal dysfunction or a significantly large tumor burden, we favor treatment with a BTK inhibitor, given the risk for tumor lysis syndrome with venetoclax-based therapy. For patients with atrial fibrillation or those on therapeutic anticoagulation, we favor a venetoclax-based regimen over a BTK inhibitor.

Future Directions

The field of CLL treatment is continuing to evolve, with several combination targeted strategies currently being investigated in phase 2 and 3 trials. On the basis

of preclinical synergy between BTK inhibitors and venetoclax, trials have been initiated with a combination of BTK inhibitors plus venetoclax, with or without the CD20 monoclonal antibody obinutuzumab. The group from MDACC reported on the combination of ibrutinib and venetoclax in 80 patients with previously untreated CLL.²⁹ Patients received ibrutinib monotherapy for 3 cycles, followed by ibrutinib in combination with venetoclax for a total of 24 cycles. In an updated analysis, the investigators reported on an intention-to-treat analysis in which the U-MRD rate in bone marrow was 56% at 12 cycles and 66% at 24 cycles.³⁰ Bone marrow U-MRD as the best response was achieved in 75% of patients. The CAPTIVATE trial evaluated a similar strategy of combining ibrutinib and venetoclax for 1 year, after which patients were randomized according to MRD status.³¹ In CAPTIVATE, the bone marrow U-MRD rate was 68% and the peripheral blood U-MRD rate was 75% after 12 cycles of the combination. Several ongoing trials are investigating triplet combinations of targeted therapies consisting of a BTK inhibitor (ibrutinib, acalabrutinib, or zanubrutinib [Brukinsa, BeiGene]) with venetoclax and obinutuzumab (Table 1). From the data reported so far, it is not clear if triplet therapy is better than doublet therapy in first-line CLL. Several ongoing randomized phase 3 studies of the first-line treatment of CLL are exploring this question with head-to-head comparisons of several doublet and triplet combinations (Table 2). The results of some of these phase 3 trials are expected in the next 1 to 2 years and will help further define the appropriate first-line targeted therapy for patients with CLL.

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