Chronic Lymphocytic Leukemia: Individualizing Treatment Approach

Presented by Andrew D. Zelenetz, MD, PhD

Abstract

A host of new therapies are now available for treating patients with chronic lymphocytic leukemia (CLL) in both the upfront and relapsed or refractory settings. Although the optimal use of these agents is still being defined, established and emerging prognostic markers aid in the selection of appropriate treatment with the best chance of success. At the NCCN 22nd Annual Conference, Dr. Andrew Zelenetz discussed the role of the CLL-International Prognostic Index for risk stratification, reviewed optimal first-line therapy options, and then presented updated clinical trial data on the novel agents being used in the relapsed or refractory setting. The hope is that chronic therapy will be replaced by combinations that provide high rates of minimal residual disease negativity with durable remissions.

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Chronic lymphocytic leukemia [CLL] is a continuum of disease. Although a number of patients will never be treated for their disease (indolent CLL; “early” asymptomatic), most patients will move on to active CLL (“later” symptomatic) or relapsed/refractory CLL (“late” active resistant stage),” stated Andrew D. Zelenetz, MD, PhD, Medical Director, Quality Informatics, Department of Medicine, Memorial Sloan Kettering Cancer Center, and Professor of Medicine, Weill Cornell Medical College. Dr. Zelenetz is Chair of the NCCN Non-Hodgkin’s Lymphomas Panel and serves on the executive editorial board of *JNCCN*.

Prognostic Markers

In addition to using the clinical staging systems for CLL (Rai and Binet systems) to determine patient risk status,

prognostic factors should also be considered. “Traditional” high-risk parameters include Rai stage, lymphocyte doubling time, beta-2 microglobulin, and the pattern of marrow involvement. *IGHV* (immunoglobulin heavy chain variable gene) mutational status, cytogenetics [eg, del(11), trisomy 12, del(13), and del(17)], and *TP53*, *Notch1*, and *SF3B1* mutations are the “modern” risk parameters.

IGHV mutation status is “critically important,” stated Dr. Zelenetz. It can be obtained with DNA sequencing, which is readily available and the standard of care, he added. In terms of the impact of *IGHV* mutation on prognosis, “Mutated is good, and unmutated is bad (associated with a poorer prognosis),” Dr. Zelenetz simplified. However, he pointed out an important single-gene exception to this rule: *VH3-21*; CLL utilizing this *IGHV* is linked to a poor prognosis regardless of the mutational status. “You have to be aware of this exception in your thinking,” he said.

Dr. Zelenetz discussed the CLL–International Prognostic Index (IPI), a new prognostic model developed by the International CLL-IPI working group (Figure 1). CLL-IPI uses 5 independent prognostic factors (*TP53* status, *IGHV* mutational status, serum beta-2 microglobulin concentration, clinical stage, and age) to stratify patients with CLL into 4 prognostic groups (low, intermediate, high, and very high risk) with different survival outcomes¹; 5-year survival rates are 93%, 79%, 64%, and 23%, respectively. “This robust model was predictive

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in both the internal and external validation,” Dr. Zelenetz noted. The proposed treatment recommendations based on the CLL-IPI suggest that patients at low risk do not require any treatment, those at intermediate risk require treatment only if symptomatic, those at high risk require treatment unless they are asymptomatic, and those at very high risk should receive treatment either in experimental protocol or with noncytotoxic drugs if possible. “We are working on a new model for the kinase era,” Dr. Zelenetz said.

Frontline Setting

Dr. Zelenetz briefly reviewed recent clinical trial data on some of the treatment options used for newly diagnosed CLL. He first discussed long-term data from 2 clinical trials that evaluated FCR (fludarabine/cyclophosphamide/rituximab) as first-line therapy.^{2,3} The final analysis of the phase III CLL10 trial confirmed that FCR remains the standard frontline therapy for fit patients with CLL.² FCR was superior to bendamustine/rituximab (BR) in terms of progression-free survival (PFS) and complete response (CR) rate. However, BR was associated with lower rates of neutropenia and severe infections in elderly patients, suggesting that it may be considered as an alternative first-line regimen in fit, elderly patients.

Long-term follow-up data from another trial (FCR 300) showed that FCR was associated with a significantly higher PFS in patients with IGHV-mutated CLL.³ Although overall, patients have done “extremely well” with FCR, Dr. Zelenetz commented,

“When you stratify these patients by whether they have IGHV-mutated or IGHV-unmutated disease, patients with IGHV-mutated disease have something that looks a whole lot like a survival plateau, and it is not trivial, at approximately 60%.” Thus, it is now mandatory to test for IGHV mutation in young, fit patients with CLL.

Dr. Zelenetz also reviewed data from clinical trials that have evaluated novel anti-CD20 antibodies in the frontline setting: obinutuzumab (CLL11 study)⁴ and ofatumumab (COMPLEMENT 1 study).⁵ The CLL11 study compared obinutuzumab/chlorambucil with chlorambucil and rituximab/chlorambucil.⁴ “This is a really interesting comparison,” according to Dr. Zelenetz. Although substantial improvement in PFS was seen with obinutuzumab/chlorambucil and rituximab/chlorambucil versus chlorambucil, only those who received obinutuzumab/chlorambucil experienced a survival advantage. “This suggests that obinutuzumab is a better anti-CD20 antibody in CLL,” he added. The results of the COMPLEMENT 1 study demonstrated that adding ofatumumab to chlorambucil improved PFS but not overall survival in contrast to obinutuzumab added to chlorambucil, which did not improve survival.⁵

Relapsed or Refractory Setting

Novel targeted agents have been used in the relapsed or refractory setting for CLL, and Dr. Zelenetz focused on 3 agents in particular: ibrutinib (Bcr tyrosine kinase inhibitor), idelalisib (PI3 kinase inhibitor), and venetoclax (BCL2 inhibitor).

In the RESONATE trial, ibrutinib was pitted against ofatumumab in previously treated patients.⁶ Despite crossover in the trial design, a “highly statistical difference” in favor of ibrutinib was noted in terms of PFS, overall survival, and response.

However, Dr. Zelenetz acknowledged that these drugs are not without toxicity; common side effects linked to ibrutinib include hemorrhage (grade 3–5 bleeding events, 6%; bleeding events of any grade, 50%) and atrial fibrillation or atrial flutter (6%–10%).⁶ “Basically, ibrutinib is an antiplatelet agent,” Dr. Zelenetz explained, “and we must be very careful when combining with antiplatelet agents.”

Sharman et al⁷ evaluated idelalisib in a phase III trial, focusing on patient subpopulations with del(17p) and other adverse prognostic factors. The

Risk Group	Treatment Recommendation
Low	“Do not touch”
Intermediate	“Do not treat” (Except symptomatic)
High	“Treat” (Except asymptomatic)
Very high ^a	“Treat in experimental protocol or with noncytotoxic drugs if possible” (No chemotherapy or chemoimmunotherapy)

^aCannot be very high risk without del(17p) to TP53 mutation.

Figure 1. Clinical application of the Chronic Lymphocytic Leukemia-International Prognostic Index (CLL-IPI). Adapted from International CLL-IPI Working Group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol* 2016;17:779–790.

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FDA approved this agent in relapsed CLL based on the results of this study.

“It didn’t matter whether you had mutated or unmutated disease; whether you had a *TP53* mutation or not; you still responded extremely well to idelalisib,” reported Dr. Zelenetz. “If you received idelalisib, you did much better with these mutations than if you were in the placebo arm.”

As with ibrutinib, the use of idelalisib is also not free of adverse effects, particularly diarrhea or colitis. Two forms of diarrhea were noted: one is self-limiting and usually appears within the first 8 weeks, and the other occurs months later and is much more serious.⁸ In addition, transaminitis may occur within the first 12 weeks of treatment and is generally reversible.⁸ In the relapsed or refractory setting, grade 3/4 diarrhea has been reported in approximately 13% to 16% of patients. “Budesonide can be very effective in the management of late diarrhea,” suggested Dr. Zelenetz. “A prophylactic dose of budesonide (3 mg) daily, I find, reduces the risk of recurrent diarrhea.”

In a phase II study, venetoclax was found to be active and well tolerated in patients with relapsed or refractory del(17p) CLL with a poor prognosis.⁹ “It works,” remarked Dr. Zelenetz, “with overall response in approximately 80% of patients.” In fact, patients seem to experience a CR extremely early. All patients who are going to respond do so by 9 months, he added, and approximately 80% of patients respond by 3 months.

However, venetoclax has been linked to the occurrence of neutropenia (40% of patients), infections (>70% of patients), and tumor lysis syndrome. Identifying patients at higher risk and initiating prophylaxis with hydration and a uric acid-reducing agent are some of the general measures used to mitigate the risk of tumor lysis syndrome associated with venetoclax. Furthermore, increasing the dose of venetoclax slowly over time (from an initial dose of 20 mg for 1 week to a gradual stepwise increase over 5 weeks [target dose of 400 mg/d]) has been found to prevent this potentially fatal complication, said Dr. Zelenetz.

The use of venetoclax in combination with rituximab was the focus of a phase Ib study.¹⁰ In this small trial of 49 patients with relapsed or refractory CLL, 25 patients (51%) experienced a CR and 28 (57%) experienced negative marrow minimal residual disease (MRD). “Everyone responded unless they had fludarabine-refractory CLL,” reported Dr. Zelenetz, “and then they had an inferior response. Time-to-event outcomes are really quite excellent, and the effects are pretty durable in a highly refractory patient population.”

Among those who had an MRD-negative CR, none experienced relapse after stopping treatment with venetoclax/rituximab. “We might have durable responses after discontinuing treatment in an MRD-negative state,” Dr. Zelenetz declared, and this strategy warrants further investigation in a randomized trial.

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