CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

The Clinical Importance of Prognostic Markers in CLL

John N. Allan, MD
Assistant Professor of Medicine
Division of Hematology and Medical Oncology
Weill Cornell Medicine
New York, New York

H&O How has the role of prognostic markers in chronic lymphocytic leukemia (CLL) changed with the transition from standard chemoimmunotherapy drugs to targeted agents?

JA Since the transition from standard chemoimmunotherapy to targeted agents has occurred, we have seen changes in the prognostic markers we assess and how we use these markers to determine which patients we consider high-risk. For example, in the era of targeted agents, negative prognostic factors such as immunoglobulin heavy chain (*IGHV*) unmutated status or the presence of deletion 11q (del[11q]) or deletion 17p (del[17p]) on fluorescence in situ hybridization (FISH) definitively steer us away from chemoimmunotherapy. These factors continue to be relevant in terms of how the patient may present initially and will influence their time to first treatment. However, as soon as patients begin to receive therapy—particularly with continuous-therapy Bruton tyrosine kinase (BTK) inhibitors—these factors are no longer associated with inferior outcomes. Of particular note, patients with *IGHV*-unmutated status are now doing just as well as those with *IGHV*-mutated status. We see the same phenomenon with del(11q); patients who have del(11q) perform just as well as patients without del(11q). We are now beginning to see that patients with del(17p) have outcomes that are very similar to those of their counterparts without del(17p) after they begin treatment.

H&O What is the usefulness of testing for prognostic markers if they do not affect outcomes with modern treatments?

JA Some might argue that prognostic factors are irrelevant if patients do just as well with targeted agents, and a targeted agent approach is being utilized. But prognostic factors provide information about both time to treatment and response to treatment. Evidence continues to mature, and we eventually will have head-to-head data that will likely identify specific patients who may do better with certain approaches. Time to first treatment refers to how long until a patient develops disease that is active enough to cause illness and require therapy. The length of this time varies widely in CLL, at anywhere from 2 years to 20 years. Knowing how long the patient may be able to defer treatment is very useful information to have for a patient who has been newly diagnosed with CLL, so we can give him or her an idea of what to expect. In addition, the presence of del(17p), complex karyotype, and certain mutations (such as *NOTCH1* mutations) also signals an increased risk for transformation to a significantly more aggressive form of large cell lymphoma. Finally, by identifying patients early on who have high-risk prognostic markers, we can set expectations early and help prepare patients for treatment decisions once there is evidence of disease activity.

After the time has come to start treatment, we want to know how good the response to treatment will be—how long can we expect the patient to experience progression-free survival (PFS)? For example, when using a fixed-duration combination such as venetoclax (Venclexta, AbbVie/Genentech) and obinutuzumab (Gazyva, Genentech), it has become clear that patients with del(17p) or unmutated *IGHV* have inferior PFS compared with patients who do not have these features. Despite this finding, the remissions are still remarkably long, patients are

able to experience a treatment-free interval, and no current evidence suggests that overall survival is decreased. This combination therefore remains a great option even for high-risk patients, although it sets a new expectation for when we may need to intervene again. In addition, there continues to be a very small subset of patients in the United States who receive chemoimmunotherapy, and prognostic marker testing is absolutely required before chemoimmunotherapy. But even when my patients are receiving targeted therapy, I always obtain information about biomarkers before making any treatment decisions.

> I think we still have much room for improvement when it comes to scoring systems in the era of targeted agents.

H&O Which biomarkers should be part of standard testing?

JA The guidelines from the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) list 3 types of tests that all patients with CLL should receive. First is an assay to sequence *IGHV* and determine the *IGHV* mutational status. Second is a test of CLL FISH cytogenetics that includes probes that cover 5 recurrent abnormalities on chromosomes 13, 12, 11, 17, and 6; approximately 80% of patients with CLL have at least 1 of these abnormalities. Finally, patients should receive next-generation sequencing to look for mutations in genes such as *TP53*, *NOTCH1*, *SF3B1*, and *ATM*.

H&O When should prognostic markers be checked in patients with CLL?

JA The iwCLL guidelines recommend that prognostic markers be checked prior to administration of any therapy. Many physicians order tests for prognostic markers at diagnosis, and I find a lot of value in this approach. Being able to identify high-risk patients affects the way we monitor these patients, and how we treat them when we see disease activity.

If the patient begins to show disease activity 5, 6, or 7 years later, I repeat the prognostic workup. This includes a new workup of CLL FISH cytogenetics and

a new sequencing panel to see if the patient has acquired any new mutations or other abnormalities.

H&O Is there still a role for prognostic scoring systems in CLL?

JA Scoring systems in CLL have evolved over the years as we have transitioned from chemoimmunotherapy to targeted agents. The International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI), which factors in age, clinical stage, serum β_2-microglobulin level, *IGHV* mutational status, and *TP53* status, is very good at stratifying patients treated with chemoimmunotherapy and identifying those at increased risk for relapse. The only real value of this system in patients who receive targeted therapy is for predicting time to first treatment.

The Four-Factor Prognostic Model CLL4, which Ahn and colleagues developed for use in CLL patients treated with ibrutinib (Imbruvica, Pharmacyclics/Janssen), factors in *TP53* status, prior treatment, β_2-microglobulin level, and lactate dehydrogenase level. This model was shown to be effective at distinguishing among patients at high, intermediate, and low risk for not responding to ibrutinib. This model was not as accurate in the setting of treatment-naive disease as in the setting of relapsed or refractory disease, so it is not a perfect tool. I think we still have much room for improvement when it comes to scoring systems in the era of targeted agents.

H&O Which trials are looking at the use of prognostic markers with novel agents in CLL?

JA Virtually all the modern studies of CLL are collecting this information, so retrospective analyses can determine how the outcomes of various patient groups differ based on specific risk factors. Now that we have decent follow-up with some of the studies of targeted agents and targeted combination regimens, we have been able to redefine what is considered high-risk. One of the features that is becoming widely recognized, and that is proving to be an important prognostic factor related to outcomes with targeted agents, is the complex metaphase karyotype. This karyotype is frequently associated with del(17p). Although guidelines do not currently recommend that oncologists test for complex metaphase karyotype, this is something I do in my practice. I find that having this information sheds a lot of light on why certain patients may be progressing sooner than expected or may exhibit resistance to certain targeted drugs.

H&O What are the most important studies that are looking at the use of targeted therapy in CLL?

JA Several large phase 3 clinical trials are looking at questions related to the optimal sequence of drugs, the optimal combination of drugs, and the use of triplet or doublet regimens vs sequential monotherapy.

The most relevant international study is CLL17 from the German CLL Study Group. This randomized trial, which is planning to enroll 897 patients, is looking at ibrutinib monotherapy vs venetoclax/obinutuzumab vs ibrutinib/venetoclax in patients with previously untreated CLL (NCT04608318). This study is recruiting patients in multiple European countries and Israel. Another international study, called GAIA/CLL13, is demonstrating the value of venetoclax-based fixed-duration approaches vs fludarabine, cyclophosphamide, and rituximab (FCR). Interim results presented at the 2022 annual meeting of the European Hematology Association (EHA) showed that fixed-duration venetoclax plus obinutuzumab, without or with ibrutinib, led to higher rates of undetectable measurable residual disease and improved PFS in younger patient populations across various risk groups compared with chemoimmunotherapy.

Several important trials are also being conducted in the United States. First is the EA9161 study from the ECOG-ACRIN Cancer Research Group, which is looking at venetoclax plus ibrutinib/obinutuzumab vs ibrutinib/obinutuzumab alone in untreated adults younger than 70 years with CLL (NCT03701282). This study has completed enrollment. Second is a counterpart study to EA9161 from the National Cancer Institute, which is comparing the same 2 regimens in CLL patients aged 65 years and older (NCT03737981). This study has also completed enrollment. Third is MAJIC, which will be comparing acalabrutinib (Calquence, AstraZeneca)/venetoclax vs venetoclax/obinutuzumab in patients with previously untreated CLL (NCT05057494). This study is not yet recruiting patients. Fourth is a study from Acerta Pharma that is comparing acalabrutinib/venetoclax vs obinutuzumab plus acalabrutinib/venetoclax vs chemoimmunotherapy in patients with previously untreated

CLL (NCT03836261). This study is currently recruiting patients and results have yet to be presented.

I expect these 6 studies will provide a great deal of understanding over the next 3 to 5 years regarding the best ways to optimize therapy for each patient.

H&O What do you see happening in the next 5 years regarding prognostic testing in CLL?

JA Over the next 5 years or so, we expect to have mature data from large clinical trials. This information should give us robust data on the best approaches for specific subgroups of patients, depending on the risk factors they have. We should be able to optimize therapy for individual patients, with clear indications regarding whether patients will require doublet therapy, triplet therapy, or just sequential monotherapy. I think that the future is very bright for our patients with CLL, and I look forward to seeing data from these exciting studies mature and be presented and published.

Suggested Readings

Ahn IE, Tian X, Ipe D, et al. Prediction of outcome in patients with chronic lymphocytic leukemia treated with ibrutinib: development and validation of a four-factor prognostic model. *J Clin Oncol*. 2021;39(6):576-585.

Eichhorst B, Niemann C, Kater A, et al. Time-limited venetoclax-obinutuzumab +/- ibrutinib is superior to chemoimmunotherapy in frontline chronic lymphocytic leukemia (CLL): PFS co-primary endpoint of the randomized phase 3 GAIA/CLL13 trial [EHA abstract LB2365]. *HemaSphere*. 2022;6(suppl 3).

Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-2760.