CLL IN FOCUS

News in the Treatment of Chronic Lymphocytic Leukemia

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Watch and Wait Remains Best Approach for High-Risk Binet Stage A Chronic Lymphocytic Leukemia

The current standard of care for patients with Binet stage A chronic lymphocytic leukemia (CLL) is watch and wait, and a new study finds that this standard applies even for patients with high-risk disease who receive chemoimmunotherapy. The study, by Dr Carmen Herling of the University of Cologne in Cologne, Germany, and colleagues, was published online in *Leukemia* on February 18, 2020.

In the phase 3 study, called CLL7, researchers from Germany, France, Austria, and Switzerland identified 800 adults with untreated Binet stage A CLL across 94 sites (NCT00275054). Of these, 201 with high-risk disease were randomly assigned either to immediate therapy with fludarabine, cyclophosphamide, and rituximab (FCR; 100 patients) or to watch and wait (101 patients). High-risk disease was defined as the presence of 2 or more of the following: lymphocyte doubling time of less than 12 months; serum thymidine kinase level above 10 U/L; unmutated *IGHV* genes; and unfavorable genetics, defined as 11q deletion (del[11q]), 17p deletion (del[17p]), or trisomy 12.

The overall response rate (ORR) in the early-FCR group was 92.7%. After a median observation time of 55.6 months, the event-free survival was significantly longer in the early-FCR group than in the watch-and-wait group (median not reached vs 18.5 months, $P<.001$). Despite these findings, the 5-year overall survival (OS) rate was not significantly higher in the early-FCR group than in the watch-and-wait group (82.9% vs 79.9%, respectively; $P=.864$).

Grade 3 to 5 adverse events occurred in 74.4% of the 82 patients assigned to the early-FCR group who received at least one dose of FCR. The most common of these were leukopenia/neutropenia or another hematologic toxicity, infection, and elevated liver enzymes or other metabolic/laboratory events. Two deaths occurred that appeared to be related to FCR.

The authors concluded that although early FCR can induce remissions in patients who have high-risk Binet stage A CLL, their data did not provide evidence to alter the current standard of care.

Idelalisib Improves Health-Related Quality of Life in CLL

The addition of idelalisib (Zydelig, Gilead) to treatment with rituximab improves health-related quality of life (HRQOL) in patients with relapsed or refractory CLL (R/R CLL), according to follow-up of an earlier study. The new analysis appeared online in *Haematologica* on February 13, 2020.

In the original phase 3 study, 220 elderly patients with R/R CLL and comorbidities were randomly assigned to receive idelalisib plus rituximab or placebo plus rituximab (NCT01539512). The addition of idelalisib to rituximab significantly improved ORR, progression-free survival (PFS), and OS. These findings, in combination with the acceptable toxicity profile of idelalisib plus rituximab, led to approval of the combination for these patients in the United States and Europe.

In the prespecified follow-up analysis, researchers led by Dr Paolo Ghia of the Vita-Salute San Raffaele University in Milan, Italy, used the 44-item Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) scale to evaluate HRQOL. This scale measures physical, functional, social/family, and emotional well-being, in addition to leukemia-specific symptoms such as fevers, chills, night sweats, nodal swelling, and fatigue.

HRQOL scores, including scores for physical well-being, functional well-being, and leukemia-specific symptoms, were better in the patients who received idelalisib/rituximab than in those who received placebo/rituximab. The patients who received idelalisib/rituximab did not, however, have better scores for social/family well-being or emotional well-being, possibly because during their long history of CLL they had reached a relatively stable emotional and social state that was no longer affected by treatment.

Improvements began as early as 4 weeks after the initiation of treatment and continued through weeks 12, 16, 20, 24, and 48. The authors noted that the early improvements in HRQOL achieved with idelalisib/rituximab are in contrast with what is seen with classic chemoimmunotherapy, in which short-term toxicity generally delays improvements in HRQOL.

Patients With CLL Not Receiving Full Benefits of Prognostic Testing

The rate of prognostic testing is low in patients with CLL, according to an interim analysis of data from a US-based registry. Even when patients undergo testing, the results often fail to inform treatment.

A registry called informCLL (NCT02582879) is the first registry to enroll patients with CLL after the approval

of novel targeted agents. Results of the interim analysis appeared online in *Clinical Lymphoma, Myeloma & Leukemia*, on October 21, 2019. Dr Anthony R. Mato of Memorial Sloan Kettering Cancer Center in New York, New York, was the first author. The analysis included data on 840 patients with CLL or small lymphocytic lymphoma (SLL) who received treatment at any of 200 centers within 30 days of enrollment. Of these patients, 459 had previously untreated disease and 381 had R/R disease. Most of the patients (96%) were seen in a community practice setting.

The researchers found that only 31% of patients had undergone testing with fluorescence in situ hybridization (FISH) for chromosomal abnormalities, 11% testing for *TP53* mutation status, and 11% testing for *IGHV* mutation status. Of the patients with positivity for del(17p) or mutated *TP53*, 34% and 26%, respectively, received chemoimmunotherapy—despite 2018 recommendations from the International Workshop on CLL stating that these patients should not receive chemoimmunotherapy. Of the patients who did not undergo FISH testing for chromosomal abnormalities or testing for *TP53* mutation status before registry enrollment, 34% and 26%, respectively, received chemoimmunotherapy.

"Results from this early interim analysis indicate that the rates of prognostic marker testing occurred in a low percentage of patient with CLL regardless of line of therapy," wrote the authors. Furthermore, they noted that the presence of high-risk features—del(17p) and mutated *TP53*—"is unfortunately not translating to choosing the optimal therapy for these patients."

Duvelisib Efficacious, Safe After Disease Progression in Relapsed/Refractory CLL

The use of duvelisib (Copiktra, Verastem) can benefit patients with R/R CLL or SLL whose disease has progressed on ofatumumab (Arzerra, Novartis), according to an extension of the phase 3 DUO study that appeared online in *Clinical Cancer Research* on January 21, 2020. Duvelisib, given orally, is a dual inhibitor of the phosphoinositide 3-kinases δ and γ.

In the original DUO study (NCT02004522), 196 patients with R/R CLL or SLL were randomly assigned to receive duvelisib or ofatumumab. Median PFS and ORR were significantly better in the duvelisib group than in the ofatumumab group, leading to FDA approval of duvelisib for these patients.

In the extension study (NCT02049515), Dr Matthew S. Davids of the Dana-Farber Cancer Institute in Boston, Massachusetts, and coinvestigators evaluated 90 patients from the ofatumumab group who crossed over to duvelisib treatment. Median follow-up was 13.5 months.

The ORR was 77% among the patients in the extension study, including those who had del(17p) or mutated *TP53*, vs 29% before crossover. The median time to response in the extension study was 2.6 months, and the median duration of response was 14.9 months. PFS was longer with duvelisib than it had been in the same patients when they were receiving ofatumumab, at 15.7 vs 9.4 months, respectively. The median OS with duvelisib was similar to what it had been in the original DUO study, at 43 months vs not reached, respectively.

The majority of patients taking duvelisib (89%) experienced grade 3 or higher treatment-emergent adverse events, such as neutropenia, diarrhea, colitis, and pneumonia. More than half of patients (52%) discontinued treatment because of adverse events.

The authors concluded that duvelisib is "effective and tolerable in difficult-to-treat patients" with R/R CLL or SLL. They said that even though ofatumumab is used less often as monotherapy than it was at the time of the study, the results may be applicable to other anti-CD20 monoclonal antibodies, such as obinutuzumab (Gazyva, Genentech).

Acalabrutinib/Obinutuzumab Combination Produces Durable Responses in CLL

A combination of acalabrutinib (Calquence, AstraZeneca) and obinutuzumab produced high ORRs and PFS rates in patients with CLL, according to a phase 1b/2 study. Previous randomized studies with earlier drugs from the Bruton tyrosine kinase (BTK) inhibitor and anti-CD20 monoclonal antibody classes did not show improved outcomes from combination treatment.

For the single-center study (NCT02296918), which appeared in the March 2020 issue of *Cancer Discovery*, Dr Jennifer Woyach from the Ohio State University in Columbus, Ohio, and colleagues enrolled 45 patients with CLL. Patients were either treatment-naive (n=19) or had R/R disease (n=26). All patients received acalabrutinib (100 mg twice daily) until progression of disease, and 6 cycles of obinutuzumab.

After a median follow-up of 39 months in treatment-naive patients and 42 months in R/R patients, the researchers found that the ORR was 95% and 92% in each group, respectively. A complete remission occurred in 32% of treatment-naive patients and 8% of R/R patients, and the 3-year PFS rate was 94% in treatment-naive patients and 88% in R/R patients.

The majority of patients in the treatment-naive and R/R groups (63% and 77%, respectively) experienced at least one grade 3 or higher adverse event. Five patients discontinued acalabrutinib because of adverse events.

The authors concluded that although this was a small study, "the results suggest that this combination of BTK inhibitor plus immune therapy may have improved outcomes compared with previously published data for acalabrutinib alone."