CLL in Focus

Highlights in Chronic Lymphocytic Leukemia From the 2020 American Society of Clinical Oncology Annual Meeting

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Venetoclax/Obinutuzumab Continues to Demonstrate Superior Efficacy

Long-term results from the CLL14 trial continue to show that fixed-duration venetoclax/obinutuzumab (VenG) continues to improve progression-free survival (PFS) compared with chlorambucil/obinutuzumab (ClbG) in patients who have previously untreated chronic lymphocytic leukemia (CLL).

For the open-label phase 3 trial, Dr Othman Al-Sawaf and colleagues randomly assigned 432 patients with previously untreated CLL and coexisting conditions to receive 6 cycles of obinutuzumab (Gazyva, Genentech) plus 12 cycles of either venetoclax (Venclexta, AbbVie; n=216) or chlorambucil (Leukeran, Aspen Global; n=216).

After a median follow-up of 39.6 months, median PFS in the VenG group continued to be superior to that in the ClbG group (not reached vs 35.6 months; hazard ratio [HR], 0.31 [95% CI, 0.22-0.44]; *P*<.001). The estimated 3-year PFS rate was 81.9% in the VenG arm and 49.5% in the ClbG arm. This benefit was consistently observed across all clinical and biological risk groups, including patients with a *TP53* mutation and those with an unmutated immunoglobulin heavy chain variable region gene (*IGHV*). PFS was also significantly longer for VenG-treated patients with mutated *IGHV* status than for those with unmutated *IGHV* status.

The rate of undetectable minimal residual disease 18 months after the end of treatment was 47.2% in the VenG arm and 7.4% in the ClbG arm. Median overall survival (OS) was not reached in either group. Second primary malignancies occurred in 36 patients in the VenG arm (17%) and 22 patients in the ClbG arm (10.3%). No new safety signals were observed at this follow-up.

Al-Sawaf O, Zhang C, Tandon M, et al. Fixed-duration venetoclax-obinutuzumab for previously untreated patients with chronic lymphocytic leukemia: follow-up of efficacy and safety results from the multicenter, open-label, randomized, phase III CLL14 trial [ASCO abstract 8027]. *J Clin Oncol.* 2020;38(15)(suppl).

Acalabrutinib Demonstrates Durable Remissions in Treatment-Naive CLL

Acalabrutinib (Calquence, AstraZeneca) produces durable remissions and has long-term tolerability in patients who have treatment-naive CLL, according to results from the phase 2 ACE-CL-001 study. The results of this study provide the longest safety and efficacy follow-up to date in patients with symptomatic triple-negative CLL, according to the investigators.

The trial included 99 patients with treatment-naive CLL or small lymphocytic lymphoma who were considered ineligible for or declined standard chemotherapy and had an Eastern Cooperative Oncology Group performance status of 0 through 2. Dr John C. Byrd and colleagues randomly assigned patients to acalabrutinib at 100 mg twice a day (n=62) or at 200 mg once a day with a later switch to 100 mg twice a day (n=37). Treatment continued until progressive disease or unacceptable toxicity.

At a median follow-up of 53 months, 85 of the patients (86%) remained on treatment. Most of the discontinuations were due to adverse events (AEs) or progressive disease, which occurred in 6 and 3 patients, respectively. The most common AEs of any grade were diarrhea (52%), headache (45%), upper respiratory tract infection (44%), arthralgia (42%), and contusion (42%). All-grade and grade 3 or higher events of clinical interest included infection (84% and 15%), bleeding (66% and 3%), and hypertension (22% and 11%). All-grade atrial fibrillation occurred in 5% of patients. Second primary malignancies, excluding nonmelanoma skin cancer, occurred in 11%. Serious AEs, which included pneumonia (n=4) and sepsis (n=3), were reported in 38% of patients.

The overall response rate (ORR) was 97%, with 7% of patients achieving a complete response (CR) and 90% a partial response. The median time to response was 3.7 months. The median duration of response and median event-free survival were not reached.

Byrd JC, Woyach JA, Furman RR, et al. Acalabrutinib in treatment-naïve chronic lymphocytic leukemia: mature results from phase II study demonstrating durable remissions and long-term tolerability [ASCO abstract 8024]. *J Clin Oncol.* 2020;38(15)(suppl).

Acalabrutinib Safer, More Effective Than Certain Rituximab-Based Regimens in CLL

Monotherapy with acalabrutinib is safer and more effective than 2 rituximab-based regimens in CLL, according to final results from the ASCEND trial.

The multicenter open-label phase 3 study enrolled 310 patients with relapsed or refractory CLL. Dr Paolo Ghia and colleagues randomly assigned patients to receive oral acalabrutinib (n=155) or investigator's choice of therapy, which consisted of rituximab plus either idelalisib (Zydelig, Gilead; IdR; n=119) or bendamustine (Treanda/Bendeka; Teva; BR; n=36).

At a median follow-up of 22 months, median PFS was longer in the acalabrutinib group than in the IdR/BR group (not reached vs 16.8 months; HR, 0.27; *P*<.0001). The 18-month OS rate was 88% for both treatment regimens. The ORR was 80% with acalabrutinib vs 84% with IdR/BR, and the ORR plus partial response with lymphocytosis was 92% vs 88%, respectively.

Common AEs with acalabrutinib included headache, neutropenia, diarrhea, and upper respiratory infection. AEs led to drug discontinuation in 16% of patients in the acalabrutinib group, 56% of those in the IdR group, and 17% of those in the BR group. AEs of interest included atrial fibrillation (6% with acalabrutinib, 3% with IdR/BR), all-grade major hemorrhage (3% with acalabrutinib, 3% with IdR/BR), grade 3 or higher infections (20% with acalabrutinib, 25% with IdR/BR), and second primary malignancies excluding nonmelanoma skin cancer (5% with acalabrutinib, 2% with IdR/BR).

Ghia P, Pluta A, Wach M, et al. Acalabrutinib (Acala) versus idelalisib plus rituximab (IdR) or bendamustine plus rituximab (BR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): ASCEND final results [ASCO abstract 8015]. *J Clin Oncol.* 2020;38(15)(suppl).

Venetoclax Plus R-EPOCH Shows Activity in Richter Syndrome

A combination of venetoclax and rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (VR-EPOCH) shows activity in Richter syndrome, according to a phase 2 study.

For the study, which Dr Matthew S. Davids presented orally, 27 patients at 3 US sites who had CLL with biopsy-confirmed diffuse large B-cell lymphoma received VR-EPOCH for 1 cycle. After blood cell count recovery, the patients underwent 5 inpatient days of accelerated ramp-up of venetoclax, followed by VR-EPOCH for up to 5 more 21-day cycles. Patients who responded to treatment went on to allogeneic hematopoietic cell transplant (alloHCT) or to daily venetoclax maintenance.

After a median follow-up of 9.3 months, the intention-to-treat analysis revealed an ORR of 59%, with 48% of patients having a CR as their best response. Among the 21 patients who started combination therapy, the ORR was 76% and the CR rate was 62%. Only 1 patient who achieved a CR experienced disease progression. The patient who has been on venetoclax maintenance for the longest remains in CR 2 years after chemotherapy. Eight patients went on to alloHCT. The median PFS and median OS were both 16.3 months.

Grade 3 or higher hematologic toxicities were neutropenia (58%), anemia (50%), and thrombocytopenia (50%). Grade 3 or higher nonhematologic toxicities included febrile neutropenia (38%) and hypophosphatemia (23%). No patients had tumor lysis syndrome with the daily ramp-up of venetoclax. Ten patients have died; causes of death were disease progression (7), sepsis (1), sudden death (1), and graft-versus-host disease following alloHCT (1).

Davids MS, Rogers KA, Tyekucheva A, et al. A multicenter phase II study of venetoclax plus dose-adjusted R-EPOCH (VR-EPOCH) for Richter's syndrome. [ASCO abstract 8004]. *J Clin Oncol.* 2020;38(15)(suppl).

Addition of Ublituximab to Ibrutinib Improves PFS in High-Risk CLL

The addition of ublituximab to ibrutinib (Imbruvica, Pharmacyclics) improves PFS in high-risk CLL, according to final results from the GENUINE study. Ublituximab is a glyco-engineered monoclonal antibody that has enhanced antibody-dependent cellular cytotoxicity.

For the study, Dr Jeffrey Sharman and colleagues randomly assigned 117 patients who had high-risk relapsed or refractory CLL with del(17p), del(11q), and/or a *TP53* mutation to receive ibrutinib alone (n=58) or ublituximab plus ibrutinib (n=59).

After a median follow-up of 3.5 years, all efficacy endpoints favored ublituximab/ibrutinib over ibrutinib; these included ORR without and with partial response with lymphocytosis (90%-93% vs 69%-78%; *P*<.05), CR/CR with incomplete blood cell count recovery (20% vs 5%; *P*=.024), measurable residual disease negativity (46% vs 7%; *P*<.0001), and PFS (not reached vs 35.9 months; HR, .455; *P*=.016). The difference in PFS was driven by patients with del(17p) or mutated *TP53*, in whom PFS was not reached vs 18.9 months (HR, .253; *P*=.004). No meaningful difference in PFS was observed for patients with del(11q). The 4-year OS rate with ublituximab/ibrutinib was 82% vs 70% with ibrutinib alone, but the difference was not statistically significant.

AEs were comparable in the 2 arms, with the exception of more infusion reactions and neutropenia in the ublituximab/ibrutinib group.

The authors added that this is the first randomized trial to demonstrate a PFS benefit with the addition of an anti-CD20 agent to ibrutinib.

Sharman JP, Brander DM, Mato AR, et al. Effect of adding ublituximab to ibrutinib on PFS, ORR, and MRD negativity in previously treated high-risk chronic lymphocytic leukemia: final results of the GENUINE phase III study [ASCO abstract 8022]. *J Clin Oncol.* 2020;38(15)(suppl).