CLL IN FOCUS

News in the Treatment of Chronic Lymphocytic Leukemia

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Complete Response Linked to Progression-Free Survival in Chronic Lymphocytic Leukemia

Progression-free survival (PFS) is longer in patients with chronic lymphocytic leukemia (CLL) who have a complete response (CR) to treatment with ibrutinib (Imbruvica, Pharmacyclics/Janssen) than in those who do not have a CR, according to an analysis that was published ahead of print in *Blood* on January 2.

For the analysis, Dr Paolo Strati and coinvestigators at the University of Texas MD Anderson Cancer Center evaluated 208 patients with previously untreated or relapsed/refractory CLL who were enrolled in a randomized phase 2 trial of ibrutinib, either alone or in combination with rituximab (Rituxan, Genentech/Biogen), between 2013 and 2017.

Among the 194 patients in whom a response was evaluable, the overall response rate was 99% after a median of 10 months, and the CR rate was 24% after a median of 21 months. After a median of 4 years, the median PFS for all 208 patients was not reached. The only factors that were significantly associated with a longer PFS at 4 years were the following: (1) absence of complex karyotype, (2) absence of del(17p)/*TP53* mutation, and (3) achievement of CR. The relationship between CR and longer PFS was also noted in a landmark analysis done at 21 months.

The authors wrote that to their knowledge, "this is the first study demonstrating that achievement of CR is a desirable endpoint for CLL patients treated with ibrutinib." Although a 2018 study failed to find an association between CR at 1 year and prolonged PFS, the authors suggested that this lack of an association might be explained by the fact that the quality of a patient's response can improve for up to 2 years after the initiation of ibrutinib treatment.

Acalabrutinib Improves PFS in CLL Compared With Obinutuzumab Plus Chlorambucil

Acalabrutinib (Calquence, AstraZeneca), either alone or in combination with obinutuzumab (Gazyva, Genentech), significantly improves PFS compared with obinutuzumab plus chlorambucil (Leukeran, GlaxoSmithKline) in patients with treatment-naive CLL, according to results from the phase 3 ELEVATE CLL TN study (Study of Obinutuzumab + Chlorambucil, Acalabrutinib + Obinutuzumab, and Acalabrutinib in Subjects With Previously Untreated CLL).

Dr Jeff P. Sharman, of the Willamette Valley Cancer Institute and Research Center and the US Oncology Network in Eugene, Oregon, presented the interim findings from this trial at the 2019 annual meeting of the American Society of Hematology. The findings are important, he said after the meeting, "because they establish acalabrutinib with or without obinutuzumab as a frontline treatment option for CLL patients requiring therapy." He added that the benefit of adding obinutuzumab to a Bruton tyrosine kinase (BTK) inhibitor vs a BTK inhibitor alone had not been evaluated.

The trial included 535 people with treatment-naive CLL who were at least 65 years old or who were younger and had coexisting conditions. Participants were randomly assigned in a 1:1:1 ratio to acalabrutinib/obinutuzumab, acalabrutinib alone, or standard treatment with obinutuzumab/chlorambucil. Crossover was allowed from control to acalabrutinib monotherapy after confirmed progression.

After a median of 28 months, the 2-year PFS rate was significantly higher with acalabrutinib/obinutuzumab (93%) or acalabrutinib alone (87%) than with obinutuzumab/chlorambucil (47%); the hazard ratios (HRs) were 0.10 (95% CI, 0.06-0.17; $P<.0001$), and 0.20 (95% CI, 0.13-0.30; $P<.0001$), respectively.

Serious adverse events (AEs) were reported in 39%, 32%, and 21% of patients in the 3 groups, respectively, and grade 3 or higher AEs were reported in 70%, 50%, and 70% of patients. Grade 5 AEs occurred in 3%, 4%, and 7% of patients.

The FDA approved the combination of obinutuzumab and ibrutinib in treatment-naive CLL in January 2019.

Ibrutinib Linked to Hypertension and Cardiovascular Events

New or worsened hypertension is more likely to develop in people who receive ibrutinib for a B-cell malignancy, according to a new study. Furthermore, people in whom new or worsened hypertension developed were more likely to experience a major cardiovascular event, defined

as arrhythmia, myocardial infarction, stroke, heart failure, or cardiovascular death.

For the study, which appeared in the November 29 issue of *Blood*, Dr Tyler Dickerson and colleagues at the Ohio State University in Columbus, Ohio, reviewed data on 562 consecutive patients at their institution who received ibrutinib for a B-cell malignancy between 2009 and 2016. More than half of the patients (62%) had hypertension, defined as a systolic blood pressure of 130 mm Hg or higher, at baseline.

After a median follow-up of 30 months, 78% of the participants had new or worsened hypertension. This change occurred early in the treatment course, with new or worsened hypertension developing in 50% of the participants after 1.8 months. The mean increase in systolic blood pressure was 5.2 mm Hg, with an increase of at least 10 mm Hg occurring in more than 80% of the patients. Among the 215 patients without hypertension at baseline, new hypertension developed in 72% while they were on ibrutinib. A multivariate regression analysis revealed that patients in whom new or worsened hypertension developed were at increased risk (HR, 2.17; 95% CI, 1.08-4.38) for major cardiovascular AEs, which affected 17% of patients in the study. Initiation of an antihypertensive agent significantly reduced the risk for a major cardiovascular AE (HR, 0.40; 95% CI, 0.24-0.66).

In a commentary that accompanied the study, Dr Inhye Ahn of the National Heart, Lung, and Blood Institute in Bethesda, Maryland, wrote that the incidence of hypertension may have been higher in this study than in previous studies because ibrutinib is now widely understood to be a risk factor for hypertension.

Ibrutinib/Venetoclax Produces Encouraging Results in Relapsed/Refractory CLL

A combination of ibrutinib and venetoclax (Venclexta, AbbVie) was well tolerated in patients with relapsed or refractory CLL, with a high rate of measurable residual disease (MRD) eradication and encouraging PFS and overall survival rates, according to the results of a phase 2 study.

For the CLARITY study (Assessment of Venetoclax in Combination With Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukaemia), which was published in the October 20 issue of the *Journal of Clinical Oncology*, Dr Peter Hillmen of St James's Institute of Oncology in Leeds, the United Kingdom, and colleagues studied the use of ibrutinib and venetoclax in 53 patients with relapsed or refractory CLL.

After 12 months of treatment, 89% of patients had responded to treatment and 51% had achieved a CR. MRD negativity was achieved in the blood of 53% of patients and in the bone marrow of 36% of patients. After a median follow-up of 21 months, disease had progressed in 1 patient, and all patients were alive. Biochemical tumor lysis syndrome occurred in 1 patient. Other AEs, which were primarily neutropenia or gastrointestinal events, were either mild or manageable.

The authors concluded that the combination of ibrutinib plus venetoclax was "well tolerated" in patients with relapsed or refractory CLL. In addition, there was "a high rate of MRD eradication that led to the cessation of therapy in some patients." Finally, the PFS and overall survival rates were "encouraging."

Study Strengthens Evidence for Acalabrutinib in Relapsed/Refractory CLL

Acalabrutinib shows efficacy, durability of response, and long-term safety in the treatment of patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL), according to a phase 1b/2 study.

For the study, which appeared in the December 26 online version of *Blood*, Dr John Byrd of the Ohio State University and coinvestigators enrolled patients with relapsed/refractory CLL or SLL. A total of 134 patients received 100 mg of acalabrutinib twice a day for a median of 41 months. The patients had received a median of 2 prior therapies.

After a median of 41 months of follow-up, the overall response rate was 94%, and responses were similar regardless of the presence of genomic features such as del(17p). Although the median duration of response and PFS were not reached, the estimated 45-month PFS rate was 62%.

Most AEs were mild or moderate; these included diarrhea (52%) and headache (51%). The most common grade 3 or higher AEs were neutropenia (14%), pneumonia (11%), hypertension (7%), anemia (7%), and diarrhea (5%).

The authors wrote that "this updated and expanded study confirms the efficacy, durability of response, and long-term safety of acalabrutinib, justifying its further investigation in previously untreated and treated patients with CLL/SLL."