TOP TAKEAWAYS IN
Chronic Lymphocytic Leukemia

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Acalabrutinib extends PFS in untreated chronic lymphocytic leukemia

Acalabrutinib alone or in combination with obinutuzumab significantly prolonged PFS compared with a chemotherapy-based chlorambucil-obinutuzumab combination for patients with previously untreated chronic lymphocytic leukemia, according to results of a phase 3 trial.

Acalabrutinib (Calquence, AstraZeneca) — a Bruton tyrosine kinase inhibitor — is approved in the United States for treatment of adults with relapsed or refractory mantle cell lymphoma.

The multicenter, open-label ELEVATE-TN trial included 535 patients with previously untreated CLL. Researchers randomly assigned patients 1:1:1 to one of three groups: chlorambucil plus obinutuzumab (Gazyva, Genentech); acalabrutinib 100 mg twice daily in combination with obinutuzumab; or acalabrutinib monotherapy at 100 mg twice daily.

Treatment continued until disease progression.

PFS by independent review committee assessment in the acalabrutinib-obinutuzumab group compared with the chlorambucil-obinutuzumab group served as the primary endpoint.

PFS in the acalabrutinib monotherapy group compared with the chlorambucil-obinutuzumab group served as a key secondary endpoint.

The trial met both of these endpoints, according to an AstraZeneca-issued press release.

The safety and tolerability of acalabrutinib appeared consistent with its established safety profile.

The topline data announcement comes about a month after AstraZeneca announced another randomized phase 3 trial of acalabrutinib met its primary endpoint.

Results of the ASCEND trial — which included patients with previously treated CLL — showed acalabrutinib monotherapy significantly prolonged PFS compared with a combination of rituximab (Rituxan; Genentech, Biogen) plus physician’s choice ofidelalisib (Zydelig, Gilead) or bendamustine.

“These findings confirm the superiority of Calquence as a monotherapy and also in combination over standard-of-care treatments for chronic lymphocytic leukemia,” José Baselga, MD, PhD, executive vice president for oncology research and development with AstraZeneca, said in the release.

José Baselga
Clinically indicated ibrutinib interruptions do not limit long-term benefit in CLL

Clinically indicated dose reductions or interruptions of ibrutinib did not appear to impact long-term outcomes among patients with chronic lymphocytic leukemia, according to results of a phase 2 prospective study published in Blood.

Ibrutinib (Imbruvica; Pharmacycics, Janssen), a Bruton tyrosine kinase inhibitor, is FDA approved for all lines of therapy in CLL. Dose modifications or interruptions commonly occur because of adverse events or before invasive procedures.

Researchers sought to examine whether these dose interruptions limit the long-term benefits of the drug.

“Most of the dose interruptions and reductions in our study were done for medically indicated reasons per the FDA label for ibrutinib, not because patients were forgetful, noncompliant or just wanted to take less drug,” Inhye E. Ahn, MD, oncologist at NIH’s NHLBI, told HemOnc Today. “My take from our data is that there are more important biological mechanisms leading to drug resistance, rather than simple drug interruptions or dose reductions.”

Ahn and colleagues analyzed 84 patients with previously untreated CLL (n = 52) or relapsed/refractory CLL (n = 32).

Eligible patients had either a TP53 aberration (n = 53) or were aged older than 65 years (n = 31).

Investigators based dose-interruption data on documented patient history, with each dose-reduction event confirmed on a review of electronic pharmacy orders and patients reporting any missed doses at each clinic visit. Specifically, ibrutinib was held for elective procedures or if grade 3 or higher adverse events occurred.

The effect of dose intensity on PFS and OS served as the study’s primary endpoints.

At a median follow-up of 5.1 years, 75 patients (89.3%) missed at least one ibrutinib dose, and 12 (14.3%) required a permanent dose reduction from full-dose ibrutinib (420 mg daily) to 280 mg daily (n = 10) or 140 mg daily (n = 2). Mean dose intensity was 94.4%.

The most common reasons for treatment breaks included elective procedures (n = 152), adverse events (n = 70) and noncompliance (n = 68).

More than half of patients (n = 57) missed ibrutinib for 8 or more consecutive days, whereas 40 missed it for 15 or more consecutive days.

Twenty-three patients experienced disease progression and 18 patients died, including 13 of disease progression.

The mean dose intensity of patients who progressed was 97.7% (range, 88.4-100).

Researchers estimated 5-year PFS of 64.6% (95% CI, 54.6-76.5) for all patients and 72.1% (95% CI, 60.7-85.7) for those who missed an ibrutinib dose for 8 or more consecutive days. Corresponding rates of 5-year OS were 79.6% (95% CI, 71.1-89.1) and 90.1% (95% CI, 82.2-98.8).

Multivariate analysis showed no association between dose intensity and PFS or OS.

Ahn and colleagues noted the high dose intensity in the study and cautioned that the findings should not be extended to general ibrutinib noncompliance.

“Stopping ibrutinib is a huge deal, particularly in patients who have genetic mechanisms of resistance,” Ahn told HemOnc Today. “I discourage holding or dose-reducing ibrutinib without having medically indicated reasons to justify continuous, full-dose therapy.” – by John DeRosier

Reference:

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Risk score predicts atrial fibrillation with ibrutinib therapy for CLL

The Italian risk score accurately predicted risk for atrial fibrillation among patients treated with ibrutinib for chronic lymphocytic leukemia, according to data from a retrospective review.

“Ibrutinib [Imbruvica; Pharmacycics] causes an increased risk for bleeding and an increased risk for atrial fibrillation; thus, treating clinicians are in a difficult position,” William J. Archibald, MD, resident physician at Mayo Clinic in Rochester, Minnesota, told HemOnc Today.

“On one hand, CLL can be very well-controlled with ibrutinib therapy with minimal side effects, but if a patient develops atrial fibrillation, combining ibrutinib and antiocoagulation could cause an unacceptably high risk for bleeding. If we have to stop ibrutinib therapy because atrial fibrillation develops, other therapies for CLL may not be as well-tolerated and the CLL may not respond to other therapies. By being able to predict which patients are more likely to develop atrial fibrillation with information that clinicians already have on hand, the treating clinician can make different treatment decisions.”

Researchers assessed three clinical prediction models — the Framingham, Italian and Shanafelt risk scores — among 298 patients (median age, 67 years; range, 35-93; 70.5% men) with CLL receiving treatment at Mayo Clinic between 2012 and 2018. Patients had a cumulative 565 years of ibrutinib exposure.

After a median follow-up 24 months (range, 0-70), 51 patients developed treatment-emergent atrial fibrillation, of whom 80% had a CHA2DS2-VASc score — an indicator of stroke risk — of 2 or higher. To prevent stroke, 40% of those patients received anticoagulation alone, 14% received antiplatelet therapy alone and 10% received both.

Most (73%) incidences of atrial fibrillation were grade 2; 25% were grade 3 or worse.

Investigators found that the Italian risk score — which uses Akaike information criteria — was the best predictor for treatment-emergent atrial fibrillation. The 2-year risk for atrial fibrillation with score 0 was 6%, followed by 8% with score 1 to 2, 26% with score 3 to 4, and 47% with score 5 or higher.

Overall, 61% of patients received medical therapy for atrial fibrillation and 31% of patients underwent interventional therapy.

Among those with atrial fibrillation, 12% permanently discontinued ibrutinib, 23% temporarily discontinued ibrutinib and later resumed the original dose, 43% continued on a reduced-dose regimen, and 22% continued the initial dose.

Investigators observed shorter EFS (HR = 2.5; 95% CI, 1.5-4.2) and shorter OS (HR = 3.5; 95% CI, 2-6.3) among patients who developed atrial fibrillation.

Two major bleeds occurred, including one in a patient receiving concomitant antiplatelet and anticoagulation therapy, and one in a patient receiving neither.

No patient with treatment-emergent atrial fibrillation experienced thrombotic stroke.

“We are hoping to look at this issue prospectively and expand on other groups’ work for having patients evaluated with echocardiography or electrocardiography prior to beginning ibrutinib therapy to see if there is any benefit in more aggressively screening patients for atrial fibrillation risk factors — especially in patients with a high score on the Italian risk model prior to beginning therapy,” Archibald said. “We are encouraged that ibrutinib can be continued through the development of atrial fibrillation and the use of anticoagulation without a significant adverse toxicity profile.”

– by Jennifer Southall


Disclosures: Archibald reports no relevant financial disclosures. Please see the abstract for all other authors’ relevant financial disclosures.
Ibrutinib plus rituximab ‘more effective and less toxic’ than chemoimmunotherapy for CLL

Ibrutinib plus rituximab improved PFS and OS compared with standard chemoimmunotherapy among patients with previously untreated chronic lymphocytic leukemia, according to results of a randomized, phase 3 trial.

“These results will fully usher the treatment of chronic lymphocytic leukemia into a new era,” Tait D. Shanafelt, MD, Jeanie and Stew Ritchie professor of medicine in the hematology division of the department of medicine at Stanford University, said in a press release. “We’ve found that this combination of targeted treatments is both more effective and less toxic than the previous standard of care for these patients. It seems likely that, in the future, most patients will be able to forego chemotherapy altogether.”

Shanafelt and colleagues randomly assigned 529 patients aged 70 years or younger (mean age, 56.7 years; 67.3% men) with previously untreated CLL in a 2:1 ratio to ibrutinib (Imbruvica; Pharmacyclics, Janssen) and rituximab (Rituxan; Genentech, Biogen) for six cycles after one ibrutinib cycle, followed by ibrutinib until disease progression (n = 354); or six cycles of chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab (n = 175).

PFS served as the study’s primary endpoint, with OS as a secondary endpoint.

Median follow-up was 33.6 months, at which time 279 patients in the ibrutinib-rituximab group (78.8%) continued on ibrutinib and 132 patients in the chemoimmunotherapy group (75.4%) continued to be monitored.

Results showed that at 3 years, ibrutinib plus rituximab conferred significantly better PFS (89.4% vs. 72.9%; HR for progression or death = 0.35; 95% CI, 0.22-0.56) and OS (98.8% vs. 91.5%; HR = 0.17; 95% CI, 0.05-0.54) than chemoimmunotherapy.

A subgroup analysis of 281 patients without an immunoglobulin heavy-chain variable region (IGHV) mutation showed better PFS at 3 years with ibrutinib and rituximab vs. chemoimmunotherapy (90.7% vs. 62.5%; HR for progression or death = 0.26; 95% CI, 0.14-0.5). Researchers observed no significant difference in PFS among 114 patients with IGHV-mutated CLL (87.7% with ibrutinib and rituximab vs. 88% with chemoimmunotherapy; HR for progression or death = 0.44; 95% CI, 0.14-1.36).

Grade 3 or higher adverse events occurred among 80.1% (n = 282) of patients in the ibrutinib-rituximab group and 79.7% (n = 126) of patients in the chemoimmunotherapy group.

Grade 3 or higher cardiac toxic effects occurred among 23 patients who received ibrutinib and rituximab, including 13 cases of atrial fibrillation or atrial flutter, compared with three patients who received

PERSPECTIVE

This study supports the continued trend away from chemoimmunotherapy for patients with CLL, given the plethora of novel agents that have been approved in the past few years. However, there are still select patients for whom chemoimmunotherapy might be beneficial.

The discussion of whether to use fludarabine, cyclophosphamide and rituximab or chemoimmunotherapy still comes up for patients with IGHV-mutated CLL. In this study, PFS was no different among patients with IGHV-mutated CLL treated with fludarabine, cyclophosphamide and rituximab vs. ibrutinib and rituximab. This is the one subgroup of patients for whom this discussion is still relevant.

Unfortunately, the study does not address whether combining rituximab with ibrutinib is necessary, as there was no ibrutinib monotherapy arm. We don’t know whether rituximab added anything because patients continued ibrutinib indefinitely anyway. We’re not sure that patients need antibody therapy with ibrutinib; this has been a topic of debate in several studies. For example, the ALLIANCE 041202 trial did not show any PFS or OS advantage with the ibrutinib-rituximab combination vs. ibrutinib monotherapy.

Continued follow-up of this study will be needed to evaluate potential long-term toxic effects and/or changes to disease biology with indefinite use of ibrutinib.

Nicole Lamanna, MD
NewYork-Presbyterian/Columbia University Medical Center
Disclosure: Lamanna reports no relevant financial disclosures.
Ibrutinib plus venetoclax safely induces remission in relapsed, refractory CLL

The combination of ibrutinib and venetoclax appeared effective and safe among patients with relapsed or refractory chronic lymphocytic leukemia, according to results of the single-arm, phase 2 CLARITY study.

Targeted therapies such as the Bruton tyrosine kinase inhibitor ibrutinib (Imbruvica; Pharmacyclics, Janssen) and the B-cell lymphoma 2 inhibitor venetoclax (Venclexta; AbbVie, Genentech) have improved survival and, in many cases, replaced chemoimmunotherapy for patients with CLL. However, these drugs seldom eradicate minimal residual disease (MRD) when used individually and typically are taken indefinitely or until disease progression.

Peter Hillmen, MBChB, PhD, and colleagues administered ibrutinib in combination with venetoclax to 53 patients (median age, 64 years; range, 31-83; 69% men) with relapsed or refractory CLL (median prior therapies, 1; range, 1-6).

Eradication of MRD, in bone marrow and peripheral blood, to fewer than one CLL cell in 10,000 leukocytes after 12 months of combination therapy served as the primary endpoint. Investigator-assessed response, PFS, OS and safety served as secondary endpoints.

Results showed that 47 patients (89%) responded to treatment after 12 months, with 27 (51%) achieving complete remission.

Twenty-eight patients (53%) achieved MRD negativity in peripheral blood and 19 patients (36%) demonstrated MRD negativity in bone marrow.

One patient experienced disease progression and all patients remained alive after median follow-up of 21.1 months.

Two patients stopped the combination at 14 months after confirmation of MRD-negative remission.

Adverse events appeared manageable and consistent with the documented history of both drugs, researchers noted. One patient experienced biochemical tumor lysis syndrome. The most common grade 3 or grade 4 adverse events included neutropenia (n = 34) and infections (n = 9).

“The observation that a significant proportion of patients experience MRD-negative remission indicates that this combination can be given for a limited period and then stopped after patients achieve a deep remission.”

PETER HILLMEN, MBCHB, PHD

References:

Disclosures: Hillmen reports honoraria, research funding and/or travel expenses from AbbVie, Gilead Sciences, Janssen Pharmaceuticals and Roche. Please see the study for all other authors’ relevant financial disclosures.

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chemoimmunotherapy, including two cases of atrial fibrillation. However, the ibrutinib-rituximab group had a lower prevalence of grade 3 or higher infectious complications (10.5% vs. 20.3%; P < .001).

“Two patients stopped the combination at 14 months after confirmation of MRD-negative remission.”

Shanafelt said. “The new treatment is both more effective and better tolerated. This represents a paradigm shift in how these patients should be treated. We can now relegate chemotherapy to a fallback plan rather than a first-line course of action.”

– by Jennifer Byrne

References:

Disclosures: Shanafelt reports grant support from AbbVie, Celgene, Cephalon, GlaxoSmithKline, Hospira, Merck, Pharmacyclics and Polyphenon E International, as well as a patent on green tea extract epigallocatechin gallate in combination with chemotherapy for CLL. Please see the study for all other authors’ relevant financial disclosures.
Acalabrutinib receives breakthrough therapy designation for CLL

The FDA granted breakthrough therapy designation to acalabrutinib as monotherapy for adults with chronic lymphocytic leukemia.

Acalabrutinib (Calquence, AstraZeneca) — a Bruton tyrosine kinase inhibitor — is approved in the United States for treatment of adults with relapsed or refractory mantle cell lymphoma.

The FDA based the breakthrough therapy designation for CLL on results of two randomized phase 3 trials.

The ELEVATE-TN trial evaluated acalabrutinib alone or in combination with obinutuzumab (Gazyva, Genentech) vs. chlorambucil plus obinutuzumab for treatment-naive patients. The ASCEND trial compared acalabrutinib with physician’s choice of two other regimens — rituximab (Rituxan; Genentech, Biogen) plus idelalisib (Zydelig, Gilead), or rituximab plus bendamustine — for previously treated patients.

Results of both trials showed acalabrutinib alone or as part of combination treatment significantly extended PFS.

In both trials, acalabrutinib exhibited a safety profile consistent with that observed in prior trials.

“Results — presented at ASCO Annual Meeting — showed more patients assigned venetoclax-obinutuzumab achieved response (85% vs. 71%; \( P = .0007 \)), complete response or complete response with incomplete hematologic recovery (50% vs. 23%; \( P < .0001 \)), minimal residual disease negativity in the bone marrow (57% vs. 17%; \( P < .0001 \)) and peripheral blood (76% vs. 35%; \( P < .0001 \)).

Median OS had not been reached in either treatment group.

The combination exhibited a safety profile consistent with the known profiles of each agent alone. The most common adverse reactions included low white blood cell count, diarrhea, fatigue, nausea, low red blood cell count and upper respiratory tract infection.

Venetoclax-obinutuzumab approved for untreated CLL

The FDA approved venetoclax in combination with obinutuzumab for patients with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma.

Venetoclax (Venclexta; AbbVie, Genentech) selectively binds and inhibits the BCL-2 protein. Obinutuzumab (Gazyva, Genentech) is an anti-CD20 monoclonal antibody.

“Venclexta plus Gazyva is the only chemotherapy-free option of fixed duration that provides durable responses to help people live longer without progression of their disease, compared [with] a standard of care,” Sandra Horning, MD, chief medical officer and head of global product development at Genentech, said in a press release. “[This] approval represents our long-standing commitment to helping people with blood cancers throughout the course of their disease, and we are excited to provide this new option for untreated chronic lymphocytic leukemia.”

The FDA based the approval on results of the randomized phase 3 CLL14 study, which included 432 patients with treatment-naive CLL and coexisting medical conditions.

Researchers randomly assigned 216 patients to 12 months of venetoclax along with 6 months of obinutuzumab. The other 216 patients received 6 months of obinutuzumab plus chlorambucil, followed by an additional 6 months of chlorambucil.

The trial met its primary endpoint of improved PFS among patients assigned the venetoclax-obinutuzumab combination (HR = 0.33; 95% CI, 0.22-0.51).

Median OS had not been reached in either treatment group.

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Median OS had not been reached in either treatment group.

The combination exhibited a safety profile consistent with the known profiles of each agent alone. The most common adverse reactions included low white blood cell count, diarrhea, fatigue, nausea, low red blood cell count and upper respiratory tract infection.
Venetoclax-ibrutinib combination effective for certain patients with CLL

High-risk and older patients with previously untreated chronic lymphocytic leukemia achieved high rates of remission with a combination of venetoclax and ibrutinib, according to results of a phase 2 study published in *The New England Journal of Medicine*.

“These efficacy results are substantially better than what has been reported with ibrutinib [Imbruvica; Pharmacyclics, Janssen] or venetoclax [Venclexta; AbbVie, Genentech] monotherapy for [patients with] CLL,” Nitin Jain, MD, associate professor in the department of leukemia at The University of Texas MD Anderson Cancer Center, said in a press release. “With monotherapy, the majority of responses have been partial, and remissions with undetectable minimal residual disease in bone marrow have been rare.”

In the investigator-initiated, open-label phase 2 study, Jain and colleagues evaluated 80 treatment-naive high-risk or older patients with CLL (median age, 65 years; range, 26-83; 57% men) enrolled at MD Anderson Cancer Center. Eligible participants had at least one of the following characteristics: chromosome 17p deletion (18%); mutated TP53 (14%); chromosome 11q deletion (25%); unmutated IGHV (83%); or age 65 years or older (54%). Thirty percent of patients were aged 70 years or older, and 92% had high-risk genetic anomalies.

Treatment consisted of 420 mg once-daily ibrutinib monotherapy for three cycles, followed by the addition of venetoclax, given in a weekly dose escalation to 400 mg once daily. Patients received the combination treatment for 24 cycles.

Median follow-up was 14.8 months. Five patients withdrew from the study before initiating venetoclax, and six discontinued treatment during the combination phase. The first three cycles of ibrutinib monotherapy induced primarily partial responses. With the addition of venetoclax, the researchers saw increases over time in the percentage of patients who attained complete remission — with or without normal blood count recovery — and remission with undetectable MRD.

After 12 cycles of the combination, 88% (95% CI, 72-97) of participants achieved complete remission with normal or incomplete blood count recovery, and 61% (95% CI, 42-77) achieved remission with undetectable MRD in bone marrow. After 18 cycles, the complete remission rate with normal or incomplete blood count recovery increased to 96% (95% CI, 80-100), and the MRD-negative rate increased to 69% (95% CI, 48-86).

Three patients completed all 24 cycles of treatment, all of whom had complete remission and undetectable MRD.

Responses occurred among older patients and across all subgroups of high-risk disease. Among those aged 65 years or older, 94% achieved complete remission or complete remission with incomplete count recovery, and 76% and undetectable MRD after 12 cycles.

Estimated 1-year PFS for 98% (95% CI, 94-11) and 1-year OS was 99% (95% CI, 96-100).

The researchers observed laboratory evidence of tumor lysis syndrome in three patients, but no patient had clinical evidence of tumor lysis syndrome.

The adverse event profile of the combination treatment appeared comparable to that of each separate medication, and included any-grade easy bruising (n = 48), arthralgia (n = 38), diarrhea (n = 33), neutropenic fever (n = 4) and atrial fibrillation (n = 12), as well as grade 3 or grade 4 neutropenia (n = 38) and grade 3 thrombocytopenia (n = 2).

Prior studies of venetoclax suggest that patients who achieve undetectable MRD with the ibrutinib-venetoclax combination will attain a long-term survival benefit, according to a related editorial by Adrian Wiestner, MD, PhD, investigator in the laboratory of lymphoid malignancies at the NHLBI.

“If we extrapolate from previous studies with venetoclax, undetectable MRD will probably predict a long period of PFS after treatment discontinuation,” Wiestner wrote. “Similarly, on the basis of experience with single-agent ibrutinib in first-line therapy, patients with detectable MRD who continue ibrutinib can be expected to do well. Extended follow-up of this important study will provide many more insights into targeted therapy of CLL.”

— by Jennifer Byrne

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Venetoclax, obinutuzumab regimen appears safe, effective for CLL

The combination of venetoclax and obinutuzumab conferred high response rates with deep remissions among patients with previously untreated or relapsed/refractory chronic lymphocytic leukemia, according to results of a single-arm, phase 1b trial published in Blood.

The regimen also appeared safe, results showed.

“The standard of care for frontline CLL has shifted from chemoimmunotherapy to ibrutinib [Imbruvica; Pharmacyclics, Janssen], which is a fantastic drug for these patients and patients with relapsed or refractory CLL,” Ian W. Flinn, MD, PhD, oncologist at Sarah Cannon Research Institute/Tennessee Oncology, and lead study author, told HemOnc Today. “One of the downsides of it is that it has to be given for as long as it is helping patients. The advantage of [the venetoclax-obinutuzumab] regimen is that you can get people off of treatment in over a year. That’s really exciting for patients because now they won’t have to stay on treatment indefinitely.”

Flinn and colleagues sought to define the maximum tolerated dose of venetoclax (Venclexta; AbbVie, Genentech) — an oral BCL-2 inhibitor — when used in combination with obinutuzumab (Gazyva, Genentech), a type II anti-CD20 antibody.

The analysis included 46 patients with relapsed/refractory CLL — 24 of whom were in the study’s dose-finding cohort and 22 in the safety expansion cohort — and 32 patients with untreated CLL — including 12 in the dose-finding cohort and 20 in the safety expansion cohort.

Patients in the dose-finding cohort had been scheduled to receive venetoclax doses ranging from 100 mg a day to 600 mg a day. However, without reaching 600 mg a day, they chose 400 mg a day as their recommended venetoclax dose. A maximum tolerable dose for venetoclax was not determined in this combination study.

Although this study used the doublet of venetoclax and obinutuzumab, the authors mentioned that recently Seymour and colleagues demonstrated the effectiveness of venetoclax with rituximab (Rituxan; Genentech, Biogen) in relapsed or refractory CLL. In addition, the authors cite a currently ongoing (CLL13; NCT 02950051) study in which researchers are comparing venetoclax plus obinutuzumab with the triplet therapy that includes ibrutinib. At this time, we do not know whether the doublet or the triplet regimen will emerge as the new standard for CLL. If, however, the triplet regimen becomes the choice, then Dr. John Byrd’s words of advice and caution, published this year in Blood, become very relevant: ibrutinib may decrease CD20 expression on CLL cells and may have the potential to antagonize antibody-directed cellular cytotoxicity, which is one of the mechanisms of action of anti-CD20 antibodies.

In my opinion the study by Flinn and colleagues is important. Their results make us think of future evolution of the therapy for CLL. Such studies, indeed, are likely to help us find the new standard therapy for this disease.

References:

Kanti R. Rai, MD
HemOnc Today Editorial Board Member
Northwell Health

Disclosure: Rai reports no relevant financial disclosures.
100 mg to 600 mg with standard-dose obinutuzumab for six 28-day cycles.

The maximum tolerated dose of venetoclax when combined with obinutuzumab, as well as safety/tolerability of the regimen in all patients, served as the study’s primary endpoints.

About 80% (n = 36) of patients with relapsed/refractory CLL and 24-month PFS. After median follow-up of 26.7 months (range, 16-39), 90.6% (95% CI, 80.5-100) of patients with previously untreated disease achieved 24-month PFS.

Overall response rate reached 95% (95% CI, 84-99) in patients with relapsed/refractory disease and 100% (95% CI, 89-100) in patients with previously untreated disease.

About 80% (n = 36) of patients with relapsed/refractory CLL and all 32 patients with untreated CLL received venetoclax at 400 mg per day — after reviewing emerging data on venetoclax dosing, researchers decided not to test the 600 mg dose. More than 90% (n = 42) of patients with relapsed/refractory CLL and all 32 patients with untreated CLL completed six cycles of the regimen.

Median treatment time with venetoclax was 789 days (range, 8,1516) among relapsed/refractory patients and 371 days (range, 314-883) for previously untreated patients.

Median relative dose intensity for venetoclax was 100% in both patient groups.

After median follow-up of 29.3 months (range, 3-55), 85.4% (95% CI, 74.5-96.2) of patients with relapsed/refractory disease achieved complete response with incomplete marrow recovery occurred in 37% (95% CI, 25-53) of patients with relapsed/refractory disease and 78% (95% CI, 60-91) of patients with previously untreated disease.

Median duration of response was 40.9 months (range, 39.9-51.8) in patients with relapsed/refractory disease and not reached in treatment-naive patients.

Results were similar among different cytogenetic groups.

Three patients with relapsed/refractory disease experienced fatal adverse events associated with treatment. These included acute respiratory failure in one patient with suspected Richter’s transformation, pneumonia in the context of metastatic squamous cell carcinoma of the lung, and pneumonia reported 3 months after the last venetoclax dose.

Venetoclax was discontinued in seven patients with relapsed/refractory disease and one previously untreated patient due to adverse events.

Common adverse events included diarrhea, infusion-related reactions, neutropenia, fatigue, nausea, cough, pyrexia and anemia.

Maximum tolerated dose was not reached, establishing 400 mg venetoclax as the recommended dose for future study.

The regimen, overall, was well-tolerated and could lead to a new standard of care for patients with CLL, Flinn said.

“I believe the safety data show that this combination can be given in the average community physician’s office,” Flinn said. “It opens up new options for treatment for patients in both the frontline and relapsed or refractory settings. Ultimately, I think this will lead to the FDA approval of this regimen for frontline therapy in patients with CLL.”

References:

For more information:
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