Imbruvica Bests Chemotherapy for Older People With Leukemia

Imbruvica-based treatment may also work better than intensive chemotherapy for younger patients.

December 5, 2018 By Liz Highleyman

The kinase inhibitor Imbruvica (ibrutinib) delayed disease progression and death more than chemotherapy for adults over 65 with chronic lymphocytic leukemia (CLL), according to a study presented at the at the American Society of Hematology (ASH) annual meeting this week in San Diego. Adding Rituxan (rituxumab) did not improve outcomes, suggesting that Imbruvica alone should be the new standard of care for this population.

Another study presented at the conference showed that Imbruvica plus Rituxan is more effective than a chemotherapy-based regimen for younger individuals who can tolerate more intensive treatment.

CLL is the most common type of adult leukemia. Nearly 21,000 people will be diagnosed with CLL and about 4,500 people will die from it this year, primarily older adults. The average age at diagnosis is around 70, according to the American Cancer Society.

CLL involves overproduction of abnormal lymphocytes, usually antibody-producing B cells. These cells can crowd out normal blood cells, leading to anemia, increased susceptibility to infections and other complications. Although traditional chemotherapy can sometimes put CLL into remission, relapse is common.

Jennifer Woyach, MD, of Ohio State University Comprehensive Cancer Center in Columbus, presented findings from a Phase III trial comparing Imbruvica alone or in combination with Rituxan versus a standard chemoimmunotherapy regimen. The study was simultaneously published in The New England Journal of Medicine.

The study included 547 patients age 65 years or older with previously untreated CLL. Two thirds were men and the median age was 71. Although they make up a large proportion of people with CLL, elderly individuals are often excluded from clinical trials because of coexisting conditions, Woyach noted. About half were classified as high risk for disease progression based on TP53 mutation, 17p deletion and other genetic factors.

Participants were randomly assigned to receive continuous Imbruvica alone or Imbruvica plus Rituxan until disease progression or unacceptable toxicity occurred, or else six monthly cycles of the chemotherapy drug Bendeka (bendamustine) plus Rituxan. Those who experienced disease progression on the chemotherapy regimen could cross over to Imbruvica.

Imbruvica inhibits Bruton's tyrosine kinase (BTK), which plays a role in the maturation of B cells, which grow out of control in people with leukemia. It was approved as first-line therapy for CLL in 2016. Rituxan is a monoclonal antibody that targets the CD20 receptor on malignant B cells. Bendeka is a cytotoxic chemotherapy drug that kills fast-growing healthy calls as well as cancer cells. Imbruvica is a once-daily pill while Rituxan and Bendeka require IV infusion.

The overall response rate, meaning a reduction in the amount of cancer, was 94 percent with Imbruvica alone, 93 percent with Imbruvica plus Rituxan and 81 percent with Bendeka plus Rituxan. However, participants who received Imbruvica alone or with Rituxan were less likely to have complete responses than those using Bendeka (7 percent, 12 percent and 26 percent, respectively) and to achieve undetectable minimal residual disease, meaning no remaining malignant cells in the bone marrow (1 percent, 4 percent and 8 percent).

Progression-free survival (PFS), meaning patients were still alive without disease progression, was longer in the two groups receiving Imbruvica. After a median follow-up period of about three years, the estimated two-year PFS rates were 87 percent with Imbruvica alone, 88 percent with Imbruvica plus Rituxan and 74 percent with Bendeka plus Rituxan. The median PFS duration was 43 months in the chemotherapy group but could not be determine in the other two groups because most participants had not yet progressed.

There were no significant differences among the groups in overall survival—90 percent or higher across the board—but it takes longer to reach this endpoint if a treatment is working well.

Imbruvica was generally safe, although side effects were common. People taking Imbruvica monotherapy or Imbruvica plus Rituxan were less likely to develop severe (grade 3 or higher) blood cell deficiencies than those treated with Bendeka plus Rituxan (41 percent, 39 percent and 61 percent, respectively). However, other side effects including infections and heart rhythm abnormalities were less common in the chemotherapy group (63 percent) than in the two Imbruvica groups (both 74 percent).

The researchers reported that fatal adverse events occurred more often than expected in the Imbruvica groups, mostly due to infections, secondary cancers or unknown causes. Life-threatening atrial fibrillation is a recognized side effect of Imbruvica. But serious adverse events were uncommon overall.

"Our results establish that ibrutinib should be a standard of care for older patients with CLL—it is more effective than the best available chemoimmunotherapy regimen," Woyach said in an ASH press release. "The findings also suggest that when designing trials for CLL in older patients, ibrutinib is the efficacy standard by which other drugs should be measured.… The study highlights the importance of doing clinical trials for older patients, because the toxicities are likely to be

different for older versus younger patients, even with the same drug."

Imbruvica for Younger Patients

Younger and healthier people with CLL have traditionally been treated with intensive cytotoxic chemotherapy-immunotherapy regimens. But another study at ASH shows that targeted therapy may be a better option for this group as well.

Tait Shanafelt, MD, of Stanford University School of Medicine, reported findings from a large Phase III study of chemoimmunotherapy versus Imbruvica plus Rituxan in 529 previously untreated CLL patients age 70 and younger. The median age was 58—more than a decade younger than those in Woyach's study. The comparison regimen consisted of the chemotherapy drugs fludarabine and cyclophosphamide plus Rituxan (FCR) taken for six months.

Again, Imbruvica plus Rituxan led to improved progression-free survival compared with the FCR regimen. The risk of disease progression or death was reduced by 65 percent in the Imbruvica plus Rituxan group. This study continued long enough to show an overall survival advantage as well, with an 83 percent reduction in mortality for those receiving Imbruvica plus Rituxan.

But here, Imbruvica plus Rituxan was associated with fewer severe side effects than the intensive chemoimmunotherapy regimen (59 percent versus 72 percent, respectively), including white blood cell loss and infectious complications. Three percent of Imbruvica recipients experienced atrial fibrillation.

"We found ibrutinib-based therapy is both more effective and less toxic than our previous best therapy for CLL patients," Shanafelt said. "These findings have immediate practice-changing implications. They establish the combination of ibrutinib plus rituximab as the most effective first-line treatment for CLL patients age 70 and younger."

Further studies are needed to determine whether Imbruvica alone works as well as Imbruvica plus Rituxan in younger and fitter patients, as it does for the older age group. In light of its side effects, another unanswered question is whether Imbruvica needs to be taken indefinitely. The fact that people treated with Imbruvica were less likely to achieve complete responses or undetectable minimal residual disease in Woyach's study suggests they may need continuous therapy to prevent relapse, she suggested. Ongoing studies are exploring whether other targeted therapies, such as Gazyva (obinutuzumab) or Venclexta (venetoclax), might lead to better outcomes when paired with with Imbruvica.

Click here for the study report in The New England Journal of Medicine.

Click here to learn more about the different types of leukemia.

Click here for full prescribing information for Imbruvica.
