A Promising New Treatment for Some People with Acute Myeloid Leukemia

Ivosidenib (Tibsovo) plus chemotherapy may soon be an option for those with leukemia that has an *IDH1* mutation.

June 2, 2022 By National Cancer Institute

Some people with an aggressive blood cancer called acute myeloid leukemia (AML) who are unable to receive intensive chemotherapy as initial treatment for this cancer may soon have a new option.

For around 6% to 10% of people with AML, the disease is driven by changes in a gene called IDH1. In a large international study of people with this form of AML who can't have intensive chemotherapy, combining a drug called ivosidenib (Tibsovo) with the chemotherapy drug azacitidine (Onureg) was substantially more effective at producing remissions than azacitidine alone. Ivosidenib blocks the activity of the protein produced by IDH1.

In the clinical trial, treatment with both drugs also improved how long patients lived overall: a median of 2 years, compared with about 8 months for those treated with azacitidine and a placebo.

Results from the trial were published April 21 in the New England Journal of Medicine.

In general, side effects weren't worse in patients who received the treatment combination. In fact, patients treated with the combination reported better quality of life during the study than those treated with azacitidine alone. The trial was funded by Servier Pharmaceuticals, the maker of ivosidenib.

One factor that complicates interpretation of these results, explained Christopher Hourigan, MD, DPhil, chief of the laboratory of myeloid malignancies at the National Heart, Lung, and Blood Institute, is that the trial overlapped with the Food and Drug Administration's (FDA) approval of the combination of azacitidine and venetoclax (Venclexta) for people with AML. Under that approval, the azacitidine–venetoclax combination can be used in people with AML who can't receive standard chemotherapy.

However, patients can receive it regardless of whether their leukemia has an IDH1 mutation.

It's always good to have more treatment options for patients, said Hourigan, who was not involved

in the trial. But these new results present a challenge, he continued, because “they don’t help me, as a leukemia doctor, know how [these two drug combinations] compare” for someone with an IDH1 mutation.

FDA is currently reviewing Servier’s application to approve the ivosidenib–azacitidine combination as an initial treatment for people with AML that has IDH1 mutations.

Balancing risk and benefit

If possible, people newly diagnosed with AML receive an intensive regimen of multiple chemotherapy drugs, with the goal of pushing the disease into a complete remission—that is, eliminating leukemia cells in the bone marrow. But these drug combinations, called induction therapy, are incredibly taxing on the body.

Most people with AML are older, explained Olatoyosi Odenike, MD, director of the leukemia program at the University of Chicago, who was not involved with the study. For these patients, “and for people with many other coexisting medical problems, the ability to survive induction therapy is low. So it [becomes] an issue of doing more harm than good,” Odenike explained.

Even in very healthy people over the age of 75, AML may not respond to induction therapy, she added.

“There are some gene mutations, some chromosome abnormalities [in] leukemia cells that we know don’t yield to intensive chemotherapy, and they are more common in older adults,” she said. “In that case, maybe you could physically be able to tolerate the treatment, but would you really benefit from it?”

In the United States, before the combination of azacitidine and venetoclax was approved, people who were ineligible for induction chemotherapy—that is, they were too sick or past the age considered safe to receive it—often received azacitidine alone, with the goal of reducing the symptoms of leukemia and extending how long they lived.

In 2019, after the current trial had begun, FDA expanded its approval of ivosidenib for people with a mutation in the IDH1 gene. The drug was approved for use alone in people age 75 or older or for those with other health conditions that would prevent them from receiving intensive chemotherapy.

This new trial was designed to see if, for this group of patients, combining the two drugs was better than azacitidine by itself.

A bomb versus a slow burn

About half of the 146 patients in the trial were randomly assigned to receive azacitidine plus ivosidenib and the other half azacitidine plus a placebo. The trial planned for people to receive at least six monthly rounds of treatment, but participants could continue therapy as long as their disease remained under control.

The main outcome of event-free survival included the time from random assignment to failure of the treatment to cause remission (measured at 6 months), relapse from remission, or death from any cause. The investigators also tracked how long people lived overall, treatment toxicities, and quality of life.

The trial began in early 2018 and stopped enrolling patients earlier than planned in mid-2021, when the data panel monitoring the study recommended it be discontinued because there were already far fewer deaths in patients in the combination arm than the azacitidine arm. At that point, participants had been followed for a median of just over a year.

After 6 months, 38% of people in the combination group had a complete remission, compared with 11% of those who received azacitidine plus placebo. Beyond 6 months, additional people in the combination group went into remission.

Such delayed responses are not uncommon with targeted drugs for leukemia, explained Prapti Patel, MD, an adjunct associate professor at the University of Texas Southwestern Medical Center and senior medical director at Servier, who was involved in another trial of ivosidenib plus azacitidine.

“I tell my patients that [standard] chemotherapy is like a nuclear bomb going off,” Patel said. “It just goes into the [bone marrow] and cleans out everything, good and bad.” The result is that, with standard chemotherapy, remissions happen rapidly, she explained.

In contrast, targeted drugs for leukemia tend not to kill cancer cells outright, she added.

Instead, such drugs stop cancer cells from growing. And it takes longer for that to happen. So while leukemia remissions caused by chemotherapy usually happen within the first month, with targeted drugs “it can take 3 months, 6 months…or even longer,” she explained.

In total, almost half of those who received azacitidine and ivosidenib had a complete remission, compared with just 15% of those who received azacitidine plus placebo. Of those who had a complete remission, more than half no longer had any trace of the IDH1 mutation in their bone marrow. Such mutation clearance is a sign that someone is likely to have a long-lasting response, explained Patel.

Over the course of the study, 28 people in the combination therapy group died (39%), compared with 46 (62%) of those who received azacitidine plus placebo.

People who received the drug combination reported that their health-related quality of life was either the same or better than it had been at the start of the study. People who received azacitidine plus placebo didn't report improvements.

Almost all trial participants experienced at least one serious side effect of treatment, including a drop in red and white blood cells. Infections were more common in people receiving azacitdine and placebo. Bleeding and differentiation syndrome (a set of potentially dangerous complications caused by the immune system) was more common in people receiving azacitidine and ivosidenib.

Many options, many questions

With these results, many oncologists who treat patients with AML "will look at this combination as an additional one that we can offer our patients," Dr. Odenike said. Patients whose cancer has an IDH1 mutation can be treated with azacitidine and venetoclax or with azacitidine plus ivosidenib, she said.

Currently, even though it's approved for use alone, oncologists "tend not to use ivosidenib by itself, because the remission rates are lower than if you give azacitidine and venetoclax," she explained.

But she echoes Hourigan's concern that "the question that's going to come up is, which [combination] is superior?" she asked. "I'd want to know that as a patient, but we don't have enough information at the moment" to say, she said. Both combinations showed similar survival benefits in randomized trials relative to azacitidine alone, but it's not possible to directly compare across studies.

For some patients, the choice may come down to which potential side effects are most concerning to them, she added.

A direct comparison may never be done, said Dr. Hourigan, especially as trials have now moved on to other research questions. "People have already moved on to triplets: there are trials testing azacitidine, ivosidenib, and venetoclax [together]," he said.

Other questions now being asked include whether adding ivosidenib to induction chemotherapy could improve the remission rate for healthier patients, explained Odenike. She and her colleagues recently completed a small trial showing this approach is safe, which is the first step to a larger study.

"There is a precedent for this [approach] in AML, such as for people with a FLT3 mutation in their leukemia," she said, explaining that "When we add a FLT3 inhibitor to intensive chemotherapy, their survival is improved."

Such trials also highlight an emerging shift in AML treatment, Patel explained. While for some

people AML is a medical emergency requiring immediate treatment—even within hours of diagnosis—others can wait about a week to have DNA sequencing done on their leukemia cells. This genetic information may let them use one of the targeted drugs already approved, or potentially join a clinical trial of a targeted treatment.

Researchers hope to shrink this sequencing window even further, said Hourigan, and to launch trials that compare the different targeted therapy options based on the genetic profile of patients' tumors with the current standard of care. Such comparisons are needed to answer the "which is best?" questions that will continue to emerge, he explained.

The newer targeted therapies may work better for some people, but they are also expensive, which can cause substantial financial toxicity, he added. "So we want to make sure we're testing them rigorously so we can use them in the most efficacious way."

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