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Venetoclax combination approved for elderly acute myeloid leukemia

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Older patients with acute myeloid leukemia (AML) often aren't healthy enough to receive intensive chemotherapy, and gentler treatments aren't very effective in treating this aggressive blood cancer.

But a new option—a combination of a standard drug and the novel agent venetoclax—has been granted accelerated approval by the Food and Drug Administration for such patients after a large, multicenter phase 1 clinical trial showed the combination had "promising efficacy" and was well tolerated in older AML patients.

"I think it's likely to become a standard for patients in this situation who have AML but can't tolerate induction therapy" with harsher chemotherapy regimens, said Anthony Letai, MD, Ph.D., a medical oncologist at Dana-Farber Cancer Institute. Letai, who has carried out key research on inhibition of the BCL-2 pathway, leading to drugs like venetoclax (Venclexta), is corresponding author of a recent report in *Blood* on the results of an industry-sponsored phase 1 clinical trial.

The FDA approval is for use of venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine for treatment of patients with newly diagnosed AML who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

The median age of people diagnosed with AML is 67. Patients who are considered fit enough are treated with "induction" therapy aimed at putting the disease in remission, followed by "consolidation" therapy

with additional chemotherapy or a stem cell transplant. If successful, that two-step process can cure up to 40 percent of patients, said Letai. "But only a minority of patients are eligible to begin with" because of advanced age or because they have other conditions, such as heart disease, that increases their risk of death.

As a compromise, these patients may be treated with lower-intensity drugs called hypomethylating agents, such as azacitidine and decitabine. Letai said these drugs are "relatively nontoxic, but not that effective." They induce remissions only in about 20 percent of patients, and often require several months of treatment to achieve remission, he said. They are rarely curative, with patients having a median survival of less than a year.

In an effort to improve this situation, the clinical trial paired hypomethylating agents with venetoclax, the first of a new class of targeted drugs called BCL-2 inhibitors that destroy cancer cells by attacking BCL-2, a "survival protein" they rely on to survive and multiply. Important advances in understanding BCL-2's role in cancer and how it could be blocked to kill cancer cells was conducted in Letai's Dana-Farber laboratory. Venetoclax, sold under the name Venclexta, was first approved in 2016 to treat certain patients with chronic lymphocytic leukemia (CLL) and its use has been expanded in those patients more recently.

Letai and Marina Konopleva, MD, Ph.D., of MD Anderson Cancer Center, in collaboration with researchers at the pharmaceutical company AbbVie, focused on how inhibiting BCL-2 in AML might be a new approach to treating the disease. Initial human trials with a BCL-2 inhibitor showed that as a single agent it had activity in patients with AML, but the effects weren't robust.

Still, the rationale was promising. So, the researchers and AbbVie

scientists created a clinical trial combining venetoclax at varying dosages with a hypomethylating drug—azacitidine or decitabine. The report in *Blood* demonstrates that the pairing of the two drugs is safe and relatively tolerable in AML patients not healthy enough for standard induction chemotherapy.

The trial included 145 patients ages 65 and above who received venetoclax and decitabine or azacytidine as initial therapy. The overall response rate—complete responses plus complete responses with incomplete blood count recovery—was 67 percent. Patients who were older (75 years or above) and who had poor-risk pathological features in their cancer cells had a CR rate of 60 percent and a CR plus CRi rate of 65 percent.

The median overall survival has not been reached for patients receiving 400 mg of venetoclax. For patients receiving all dosages, median overall survival was 17.5 months.

Also encouraging, said Letai, was that responses occurred more rapidly with the combination therapy than is typical with hypomethylating agents alone.

A phase 3 trial that is underway is comparing venetoclax and azacytidine with azacytidine as a single agent.

This trial was supported by AbbVie and Genentech, which are jointly developing venetoclax.

The FDA approval "marks a significant advance for people with acute myeloid leukemia, a highly aggressive and difficult-to-treat blood cancer," said Sandra Horning, MD, chief medical officer at Genentech.

More information: Courtney D. DiNardo et al, Venetoclax combined

with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia, *Blood* (2018). DOI: 10.1182/blood-2018-08-868752