Venetoclax added to standard treatments shows promise in high-risk myeloid blood cancers

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The novel oral drug venetoclax can be safely added to standard therapies for some high-risk myeloid blood cancers and in early studies the combination shows promise of improved outcomes, say scientists from Dana-Farber Cancer Institute.

Venetoclax targets cancer's survival proteins, making them more vulnerable to treatments that cause cancer cells to self-destruct. It is the first in a new class of drugs called BCL-2 inhibitors and was first approved in 2016 for certain patients with chronic lymphocytic leukemia.

At the virtual 62nd American Society of Hematology (ASH) Annual Meeting, Dana-Farber's Jacqueline Garcia, MD, reported on two studies examining the safety and efficacy of combining venetoclax with standard treatments for high-risk patients with myeloid blood cancers such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

In one study, venetoclax was added to the standard chemotherapy administered to patients with AML or MDS prior to receiving reduced intensity conditioning stem cell transplantation. Older patients or those with co-morbidities are commonly recommended for reduced intensity conditioning transplants because they are less toxic to patients. Reduced intensity conditioning chemotherapy is given to deplete the immune

system of the patient (recipient) to prevent rejection of the donor stem cells (transplant). However, reduced intensity conditioning chemotherapy approaches are associated with high risk of disease recurrence. Because outcomes are poor in patients with myeloid blood cancers who relapse following transplantation, the investigators proposed adding venetoclax to the chemotherapy that is designed to kill the AML or MDS cells before the patient receives a transplant to restore the blood-forming and immune systems. The hope was that venetoclax would make the pre-transplant chemotherapy, consisting of the drugs fludarabine and busulfan, more effective—lessening the risk of relapse.

To test this strategy for efficacy and safety, the combination was given to 22 patients ranging in age from 25 to 71, who had AML, MDS, or MDS/MPN. Of these patients, 35% had intermediate-risk disease and 65% had adverse risk disease.

Garcia and collaborators reported that all 22 patients engrafted donor cells (had restoration of count recovery after transplant) and no serious additional toxicities were observed with the addition of venetoclax. Further, graft-versus-host disease (GVHD) rates were not increased with the addition of venetoclax. At the time of this analysis, seven of the 22 patients relapsed and five of them died. Median survival of the living patients has not been reached, but the 6-month overall survival for the cohort is 84% and progression-free survival is 76%. Overall, results have been encouraging for a very high risk patient population.

Garcia noted that the addition of venetoclax did not result in any increased toxicity. The combination of venetoclax, fludarabine, and busulfan "demonstrates promising clinical activity supporting further evaluation for high risk disease features," she said.

In a second study reported by Garcia, venetoclax was combined with the drug azacitidine in treating patients with higher-risk MDS requiring

treatment and not immediately undergoing transplantation at time of study start. Azacitidine is known as a hypomethylating agent—a drug that increases the expression of tumor-suppressor genes to slow the growth of cancer cells. However, azacitidine alone has a low overall response rate in MDS and median overall survival is around 15 months.

The researchers noted that venetoclax has shown synergistic activity with hypomethylating agents in laboratory studies. This combination was recently FDA approved for the treatment of untreated AML in patients ineligible for intensive chemotherapy. To test the safety and efficacy of this combination in humans, investigators administered it to 57 patients with high-risk MDS who had not previously been treated. The patients ranged in age from 26-85 years of age, with a median of 71.

Results showed an impressive overall response rate of 77%, including complete remission in 42% and marrow complete response rate of 42%. Median overall survival was not reached; median duration of response was 14.8 months. Median progression-free survival was 17.5 months.

MDS patients commonly report fatigue and poor quality of life due to underlying disease. The study also evaluated patient-reported outcome of the population while on treatment. The researchers said physical functioning was maintained through 48 weeks of treatment confirming tolerability of therapy. In addition, clinically meaningful improvement in fatigue and shortness of breath was achieved by the beginning of cycle 5 and was maintained through week 48.

The most common adverse events were constipation, neutropenia, and nausea. The most common serious adverse event was neutropenia with fever, at 42%. Prophylactic antibiotics were required to help reduce complications.

Garcia and colleagues concluded that the combination of venetoclax and

azacitidine "demonstrates promising efficacy, including response durability, and an acceptable safety profile for patients with high-risk MDS." A phase 3 clinical trial (VERONA) was launched comparing azacitidine plus venetoclax to azacitidine plus placebo for the treatment of frontline higher risk MDS based on these encouraging data.

More information: These presentations are scheduled for Session 721, Abstract 190 on Saturday, Dec. 5 at 3:15 p.m., and Session 637, Abstract 656 on Monday, Dec.7 at 3:15 p.m. EST.

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