Venetoclax plus azacytidine, venetoclax plus decitabine or venetoclax plus low-dose cytarabine; how do you determine which combination therapy to use on your patients with AML?

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Hi, welcome to *Managing AML*. I'm Dr. Brian Jonas. I am frequently asked, "How do you determine which combination to use on your patients?" What is being referred to here is the FDA-approved combinations of azacitidine plus venetoclax, or decitabine plus venetoclax, or low-dose cytarabine plus venetoclax.

This is an interesting question. All three of them are approved by the FDA. The azacitidine-venetoclax combination was explored in the VIALE-A trial which showed superiority over azacitidine alone. The decitabine-venetoclax combination was actually explored in the Phase Ib trial that led to the launching of the Phase III trial, so it hasn't been directly compared head-to-head in a placebo-controlled way. The decitabine-venetoclax combination in the Phase Ib trial produced very similar results to what you saw with azacitidine-venetoclax. The low-dose cytarabine combination with venetoclax was evaluated in the VIALE-C trial and showed with longer follow up apparent superiority over the low-dose cytarabine alone, although the initial analysis was not necessarily statistically significant. Nevertheless, all three of them represent approved and good options for patients who are 75 or older with newly diagnosed untreated AML, or those that are younger than 75 with certain comorbidities that make them poor candidates for induction chemotherapy.

Actually, back to the actual question, the azacitidine-venetoclax combination has some preclinical data. Some of our colleagues, for example, Dr. Pollyea, University of Colorado, has done some interesting work with his colleagues there looking at the effect of the azacitidine-venetoclax combination on leukemia stem cells, and this seems to have activity against those population. The leukemia stem cell population is what is really thought to be the root cause of the disease, so treatments that kill the leukemia stem cell population would be hypothesized to potentially have better outcomes. Such studies have not been done with decitabine combinations, and so in some people's opinion, that might be a justification to use azacitidine-venetoclax over decitabine-venetoclax.

Another possible rationality in azacitidine-venetoclax over decitabine-venetoclax is the VIALE-A trial, which proved the superiority of azacitidine-venetoclax over azacitidine-placebo, versus the decitabine-venetoclax combination which doesn't have a randomized trial showing its superiority. This is reminiscent of the azacitidine versus decitabine argument in MDS.

Now, on the other hand, azacitidine is a 7-day, every 28 days of treatment. Mostly IV, but can be given subQ, whereas decitabine is a 5-day schedule, every 28 days. In my practice, sometimes patients who are perhaps older, more difficult for them to get to the infusion center, maybe they live further away. Sometimes I'll offer those patients decitabine and maybe that's going to help them have improved quality of life by fewer trips to the infusion center. That might be one way to differentiate.

Now, in my practice, we don't use a lot of low-dose cytarabine due to some challenges with compounding and so on. That being said, it is available and I believe that a good group of patients to consider that combination for are patients who had prior HMA exposure. The VIALE-C trial, which looked at low-dose cytarabine-venetoclax versus low-dose cytarabine, prior HMA was allowed. They didn't do as well as patients who are HMA naive, but at least there was some activity in that population. The activity of azacitidine-venetoclax with prior AZA-decitabine or decitabine-venetoclax with prior AZA-decitabine, this is not well established, as these patients were not eligible for the Phase Ib or the VIALE-A trial. That might be one population that I might consider starting with low-dose cytarabine-venetoclax.