An overview of the recently approved combination of venetoclax with azacitidine or decitabine or low-dose cytarabine and where this new option fits in the current treatment paradigm

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Welcome to *Managing AML*. I am Dr. Harry Erba. Today, I would like to discuss the recently approved combination of venetoclax in combination with azacitidine or decitabine or low-dose cytarabine and where this new option fits in the current treatment paradigm.

Venetoclax is an oral BCL2 inhibitor that had, until recently, only been approved for treatment with the lymphoid malignancy chronic lymphocytic leukemia. BCL2 inhibition has also been investigated in acute myeloid leukemia. As a single agent in a phase I clinical trial, there was little activity, with less than 20% of patients having a response. However, phase 1B studies have investigated the combination of venetoclax with other standard of care agents in patients who are older than 75 and unfit for intensive chemotherapy. Venetoclax has been combined in one phase 1B study with either azacitidine or decitabine, or in a separate study with low-dose cytarabine. The population of patients who received azacitidine and venetoclax had a median age of 76 with patients up to the age of 90 years; 50% of patients in the entire cohort had poor-risk cytogenetic profiles, 20% to 25% of patients had p53 mutations. However, it should be kept in mind that in order to qualify for the study and begin therapy, the white blood cell count had to be under 25,000. In fact, only about 10% of patients received hydroxyurea to get the white blood cell count that low; one-third of patients had AML with only 20% to 30% blasts. Azacitidine was combined at full dose, 75 mg/m^2/day for seven days, with venetoclax 400 mg daily. Venetoclax 400 mg daily was combined with the decitabine at full dose at 20 mg/m^2 daily for five days. The ramp up of the venetoclax was quite quick at 100 mg the first day, 200 mg the second day, and 400 mg the third day. Higher doses of venetoclax were assessed in the phase 1B study but not shown to be beneficial. The overall response rate seen with venetoclax and azacitidine among 67 patients unfit for chemotherapy, either by age or comorbidities, was 61%. With decitabine, the overall response rate was also 61%. The majority of patients have a CR, with the remainder having CRh. The median time to achieving that remission was one month with azacitidine and 1.9 months with decitabine. The overall response rate in the separate study with low-dose ara-C and venetoclax was only 42%. However, it should be pointed out that some of the patients in that clinical trial had received prior hypomethylating agents for myelodysplastic syndrome. In a phase 1B study, some patients were able to go on to allogeneic stem cell transplantation even though they were not felt to be fit or candidates for that prior to the treatment of their acute myeloid leukemia.

In terms of toxicity, the one to be most careful of, in my opinion, is myelosuppression. Venetoclax will contribute to neutropenia. The response rates are quite high and occur early. Therefore, if a patient receives their first cycle of an HMA with venetoclax and has persistent cytopenias at day 28, one should not assume lack of activity. Instead, a bone marrow biopsy needs to be done at that early timepoint to assess for response. If there has been response but marrow hypoplasia, the venetoclax should be held until blood counts recover. If neutropenia tends to be a problem with ongoing therapy, consideration should be given for dose reduction and intermittent holding of venetoclax. It should be pointed out that these patients were actually treated in the hospital for at least the first cycle during the ramp up; however, no significant tumor-lysis syndrome was seen. There are also a number of drug-drug interactions of which the prescriber needs to be aware. In terms of early mortality, it was quite low, less than 5%. So the benefit of venetoclax in combination with a hypomethylating agent, in my opinion, is two-fold. First, the response rates are much higher than what we had seen with either agent alone, about 20% with an HMA and 20% with venetoclax, but if you look at CR rate alone, it was close to 40% with the combination of an HMA with venetoclax. Furthermore, the responses were achieved quickly, which is not always seen with an HMA alone. So I believe this is the clinical benefit for our patients since they may have less risk than that of infectious complications or requiring transfusions.

These studies have led now to phase 3 studies comparing azacitidine to azacitidine with venetoclax or low-dose cytarabine to low-dose cytarabine with venetoclax. The primary endpoint of the phase 3 studies is overall survival. In the phase 1B studies, the median overall survival with an HMA and venetoclax was approximately 15 months. In summary, I believe the addition of venetoclax to a hypomethylating agent does provide benefit in terms of higher degree of response, more rapid responses – which can be of clinical benefit for older patients who are not fit for chemotherapy – and median survival over one year. Nonetheless, we need longer follow-up and phase 3 studies to evaluate whether this regimen is also associated with a survival benefit and improvement in quality of life.