ManagingAML

High Rate of IDH1 Mutation Clearance and MRD Negativity in Patients with IDH1 Mutant Newly Diagnosed Acute Myeloid Leukemia Treated with Ivosidenib and Azacitidine

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The background to this study is that we know that in patients with relapsed and refractory acute myeloid leukemia, the IDH1 inhibitor ivosidenib leads to rates of complete remission and complete remission with partial hematologic recovery of approximately 30%, with the duration of response that approaches six months. What we then wanted to do was see what happens if you move the IDH1 inhibitor to the upfront setting, to patients with newly diagnosed AML. That actually was done in a small subset of patients treated on the original phase 1/2 study, and ivosidenib actually as a single agent has FDA approval for newly diagnosed IDH1 mutant AML and patients who are older than 75 or unfit to get standard induction chemotherapy. The next group of questions is, what happens if you combine the IDH1 inhibitor ivosidenib with our standard hypomethylating agent or one of the two standard hypomethylating agents which is azacitidine? So, that's the background to this study. What's interesting is that when you do make this combination (1) there don't seem to be any new safety concerns and (2) that remission rate that you get with single-agent ivosidenib, when you combine azacitidine and ivosidenib together, the overall response rate becomes much, much higher, it's about 78%, and the rate of complete remission and complete remission with partial hematologic recovery also increases dramatically from what you would expect from ivosidenib alone or azacitidine alone, and it increases up to about 70%.

I think this is very, very important because it shows us that you can give ivosidenib and azacitidine together in a safe manner. It also provides in these 23 patients some initial look that the combination is going to be more effective than either agent alone. Really, the definitive answer to whether the combination of ivosidenib and azacitidine is superior to azacitidine alone is going to come once the randomized placebo-controlled phase 3 AGILE trial is reported, and that's a randomized phase 3 international trial again, placebo-controlled where patients are being randomized to receive ivosidenib and azacitidine versus azacitidine alone. That trial is primarily occurring at this point outside of the United States, but we're eagerly awaiting the results. In terms of how I think about this combination as well, I always think about what about measurable residual disease? That is, these patients may have less than 5% blasts, but can you identify any hint of leukemia by very sensitive methods such as flow cytometry or next-generation sequencing? And the interesting thing about the combination of ivosidenib and azacitidine is that it leads to clearance of measurable residual disease in the vast

majority of patients who achieve a complete remission or a complete remission with partial hematologic recovery, really showing, I think, the efficacy of this combination therapy. However, because the trial is only in 23 patients, and we don't have results of a randomized phase 3 trial yet, I'm not yet going to be giving ivosidenib and azacitidine in combination to my patients. I'm going to wait for the results of the randomized phase 3 trial, but I'm certainly hoping that that trial is going to be positive. Thank you very much for your attention.

Reference:

Daigle SR, et al. High Rate of IDH1 Mutation Clearance and Measurable Residual Disease Negativity in Patients with IDH1-Mutant Newly Diagnosed Acute Myeloid Leukemia Treated with Ivosidenib (AG-120) and Azacitidine. Abstract 2706. ASH 2019. https://ash.confex.com/ash/2019/webprogram/Paper122590.html