ManagingMDS
Myelodysplastic Syndrome Educational Resource

Combination of oral cedazuridine and decitabine, known as ASTX727, in patients with MDS

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Hello, my name is Guillermo Garcia-Manero, and I'm a Leukemia Attending Physician at the University of Texas MD Anderson Cancer Center. Today, I'm going to discuss a new agent for patients with MDS known as ASTX727 - that is a combination of oral cedazuridine and decitabine. This new agent basically is an oral formulation of decitabine, a very well-known hypomethylating agent, that is approved for patients with MDS and acute myelogenous leukemia (AML). This drug actually combines two compounds, one is the decitabine itself and then a second compound is the cedazuridine that is cytidine deaminase inhibitor. So, cytidine deaminase are the catalytic activities that basically degrade decitabine when you take it per mouth. So basically by combining the decitabine with the inhibitor, we have been able to develop a drug that has identical pharmacological and pharmacodynamic profile of that of IV decitabine.

The studied that led to the approval are basically two, one actually came out the first week of August in the journal *Blood* and this was a phase I/II of ASTX727. In that original study, what we did was to look at different ratios of the decitabine with the cedazuridine to determine what will be the ratio that will basically translate into the closer pharmacological profile to that of IV decitabine. We basically achieved that on this phase I trial and then we moved into a second study, that was the true registration trial of this drug that is known as the ASCERTAIN trial. It was presented by me at this past ASH meeting, and basically what we did was to randomize patients to two different sequences of the oral decitabine versus IV decitabine. The study is complex but basically what we did was to randomize patients to either the first month received the IV decitabine or followed by the oral decitabine combination or the reverse, start with the oral followed by the IV, and the idea here was basically to compare the PK-MPV profile of the IV form versus the oral form of decitabine in each patient. The data was very robust, showing almost a 99% concordance between the pharmacological profile of this drug. The pharmacodynamic profiles also were basically identical and this actually led to the approval by the US FDA of this compound, basically based on the similarity of the pharmacological characteristics of both drugs. At ASH this year, we expect also to see data on the clinical activity of this compound followed by an important manuscript beyond the one that I just mentioned in *Blood*.

The key findings of this trial basically, again, is that this drug has clinical activity as significant or more than that of decitabine. This will be updated, as I said, at ASH, hopefully this year. The main issue is that this drug pharmacologically is basically identical to that of IV decitabine. The patient population that we tried here were patients basically that were on-label for the standard IV decitabine and this basically will allow you, for those physicians that use decitabine, to start using this oral form immediately, as we expect that this drug actually will be in the market pretty soon. We are very excited about this compound, not only because it's the first oral hypomethylating agent that is approved so, as you know, azacitidine-decitabine are the two hypomethylating agents that we commonly use both in MDS and AML and, of course, an oral form would be really transformative because patients have to come five to seven days every month for as long as these drugs work and sometimes it can be for many years, but also because an oral approach is going to allow us to basically develop multiple oral combinations, let's say with agents like venetoclax or IDH inhibitors, FLT-3 inhibitors, many of those compounds are oral, and we see in the future total oral therapies for patients with MDS and AML. That, of course, will have to be studied in the context of clinical trials. So to summarize, basically, this compound ASTX727, and the commercial name is going to be INQOVI, is an oral combination of cedazuridine and decitabine with identical pharmacological profile of that of IV decitabine, and in my opinion, should supplant IV decitabine as soon as it's available for our patients and is going to be a great asset for our patients.

References:

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3. US Food and Drug Administration. FDA approves oral combination of decitabine and cedazuridine for myelodysplastic syndromes [press release]. July 27, 2020. Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-oral-combination-decitabine-and-cedazuridine-myelodysplastic-syndromes. Accessed August 31, 2020.