
Development of a Novel Next-Generation Sequencing (NGS)-Based Assay for Measurable Residual Disease (MRD) in FLT3-ITD AML and Its Potential Clinical Application in Patients Treated with Chemotherapy Plus FLT3 Inhibitors

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Welcome to *Managing AML*. I am Dr. Mark Levis, and I am live at the 60th ASH Conference in San Diego, California. Today, I am going to be reviewing an abstract which looks at the development of a novel next-generation sequencing based assay for MRD in FLT3-ITD AML and its potential clinical application in patients treated with chemotherapy plus FLT3 inhibitors.

MRD is a very hot topic in AML right now. If we can identify those patients who have detectable or persistent residual disease, when they are in remission, we can identify the patients that need additional therapy such as allogeneic transplant or maintenance therapy with a FLT3 inhibitor. The technical problem in identifying the presence of an ITD mutation has confounded us for quite some time. What we are looking at are FLT3-ITD mutations. These are the most common FLT3 activating mutations that are associated with a poorer prognosis and they're the patient population that we are directing the development of FLT3 inhibitors at. This particular assay is a combination of PCR and next-generation sequencing. Each of those modalities, PCR and next-generation sequencing, are insufficiently sensitive to pick up a FLT3-ITD mutation at a low level. What this assay does is also similar to some assays being developed around the world. You first PCR up the entire region of interest, which is the juxtamembrane domain of FLT3, amplify it briefly, then chop it up and put it on an illumina platform and analyze it by next-generation sequencing. The result is a highly sensitive assay that picks up the presence of a FLT3-ITD mutation at around 3 cells in 10,000 or less. That is sensitive enough. We first used cell lines to develop this assay, just spiking in mutant DNA into normal DNA, and getting a linear result. But then, coming up with this assay, we wanted to actually apply to clinical samples. We took a series of patient marrow samples. These are patients that were as uniform as possible. There was a total of 17. These are patients with the FLT3-ITD mutation. They all had an NPM1 mutation. They all had normal karyotype. They were all treated with intensive chemotherapy-based regimen and they all achieved remission after that first round of chemotherapy. All of these patients were taken to allogeneic transplant. The interesting point about this group of 17 patients is half of them were actually treated with chemotherapy plus a FLT3 inhibitor. The other half just received chemotherapy.

When we looked at the level of measurable residual disease in the remission specimens of these 17 patients, we were able to detect it in virtually all of them; however, it was the level of measurable residual disease that caught our attention. The patients who had received treatment with chemotherapy plus a FLT3 inhibitor had a level of MRD more than 10-fold less than those who received chemotherapy alone, implying that in fact the combination was getting deeper remissions. This actually helped explained a finding out of the RATIFY trial in which patients who received chemotherapy plus midostaurin, who then went to an allogeneic transplant, had much better outcomes than patients who received chemotherapy alone and went to allogeneic transplant. The best explanation for that everybody realized was they had a deeper remission, but this study actually is the first time to demonstrate that deeper remission in response to the combination therapy.

Reference

Levis M, Shi W, Chang K, et al. Development of a Novel Next-Generation Sequencing (NGS)-Based Assay for Measurable Residual Disease (MRD) in FLT3-ITD AML and Its Potential Clinical Application in Patients Treated with Chemotherapy Plus FLT3 Inhibitors. ASH 2018. Abstract 1459.