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What is the emerging role of FLT3 inhibitors in the treatment of newly diagnosed AML?

Welcome to *Managing AML*. I am Dr. Richard Stone. I am frequently asked, "What is the emerging role of FLT3 inhibitors in the treatment of newly diagnosed AML?" In the spring of 2017, we were fortunate for the first time in many years to have a new drug approved for acute myeloid leukemia (AML). That drug is midostaurin and it is approved to be used in conjunction with induction chemotherapy (daunorubicin and cytarabine) followed by in conjunction with consolidation chemotherapy (high-dose ara-C) in the treatment of fit AML adults with newly diagnosed mutant FLT3 AML. How did we get to this happy point? Well, it has been known for almost 20 years that about 30% of patients with acute myeloid leukemia have a FLT3 mutation in their blasts. FLT3 is a transmembrane tyrosine kinase that signals, with the help of a ligand called the FLT3 ligand, to cause proliferation of leukemic stem cells. Patients who harbor one of the two types of the FLT3 mutations have an adverse prognosis. The two types of FLT3 mutations are an internal tandem duplication mutation, which is a duplication of between 1 to 3 and 100 amino acids in the juxtamembrane region of this transmembrane tyrosine kinase, or a point mutation in the tyrosine kinase domain of the active site of the enzyme.`` These two mutations cause spontaneous dimerization without need for ligand binding, and again as I said, when a patient with AML has one of these two mutations in their blasts, they have an adverse prognosis. That is particularly true for patients with AML with a high degree of FLT3-ITD mutation allele compared to the wild-type allele.

It is a common mutation, it is an activating mutation, and it is associated with a poor prognosis. Once those three facts were known, the AML therapeutic development community thought it might be possible to benefit AML patients by using small molecules that could inhibit this activated enzyme. It took a long time to get to the point where we could actually safely combine a FLT3 inhibitor with chemotherapy. It was first hoped that you could get a lot of bang for your buck using a single-agent FLT3 inhibitor. I studied midostaurin about 15 years ago and it did have some activity in the relapsed mutant FLT3 AML setting, but it was not sufficiently profound to expect that it would be a useful agent as a single agent in that setting.

We later showed that it was possible to safely combine midostaurin, the first-generation FLT3 inhibitor, with chemotherapy in newly diagnosed patients with AML. The results in the phase 2 trial that showed that it was safe gave some suggestion that patients with FLT3 AML might be doing a little bit better than we expected when they got both 3 and 7 and midostaurin. That

was the genesis of the big trial called CALGB 10603, or RATIFY, which was a fairly simple design but a very complicated trial to go through with, because we had to screen 3,300 patients with AML to find the 714 with the FLT3 mutation who were willing to be randomized to chemo alone or chemo plus midostaurin. The primary endpoint of this trial was overall survival. Fortunately, as of the end of 2015, we learned that those who were exposed to midostaurin plus chemotherapy had a 23% reduction of the risk of death compared to the group who were exposed to placebo plus chemotherapy. Many of the patients on that trial had transplants. About a quarter of them had transplants during first remission, and first remission transplant for FLT3 AML has been an emerging standard of care for the past 5 to 10 years. The fact that the trial met its primary endpoint of improving overall survival when midostaurin was combined with chemotherapy in upfront mutant FLT3 AML ultimately allowed the FDA to approve this combination for the treatment of such patients.

Right now, we have a new standard of care, and the approval is for patients who have mutant FLT3 AML with either of the two types of FLT3 mutations, who are fit for chemotherapy, so there is no upper age restriction. You get chemotherapy induction, and beginning the day after the chemotherapy finishes, you take midostaurin 50 mg twice a day for 14 days. If you go into remission, you get post-remission chemotherapy, usually in the form of high-dose ara-C. You get midostaurin on day 8 through 22, 14 days after the chemotherapy is administered. This led to, as I said, a reduction of likelihood of death. It also led to about a 7% improvement in long-term disease-free survival and long-term overall survival. If you look at 4-year survival rates, you get about 44% in the placebo group and about 51% in the midostaurin group. We have improved the cure rate by about 7%, which I think is somewhat modest mathematically, pretty exciting from a therapeutic standpoint.

Now the issue is: what is the best FLT3 inhibitor to use? In upfront AML, we do not have any other ones right now, but the question for the treating community will be, in the future, is a more specific FLT3 inhibitor a better drug to combine with chemotherapy in the upfront setting than midostaurin, which is really a pan-kinase inhibitor? It inhibits a lot of other enzymes beside FLT3, which might be a good thing or might not be relevant, we have to see that in the future. The bottom line is new standard care chemotherapy plus midostaurin in upfront mutant FLT3 AML and with important questions about how does the drug really work? Would it be better to have a specific FLT3 inhibitor? Should we give it after transplant if a patient gets transplanted in first remission? So, like any good study, many more questions are generated, but at least we do have a new therapy for patients with AML. Thank you for viewing this activity.