What is the role of emerging targeted therapies in AML?

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Welcome to *Managing AML*, I am Dr. Naval Daver. I will be talking about the role of emerging targeted therapies in acute myeloid leukemia. There have been a number of new drugs that have moved into the therapeutic arena for acute myeloid leukemia in the last four to five years. Of these, a large majority have been agents that we call targeted therapies or tyrosine kinase inhibitors. These tyrosine kinase inhibitors target particular receptors, or mutations, that have been identified on acute myeloid leukemia blast cells and progenitor cells. By targeting these abnormal cells, they help reduce the acute myeloid leukemia burden and try to get patients into deeper remission.

The first major group of these agents is the drugs that we call FLT3 inhibitors. FLT3 mutations are one of the most common mutations seen in AML. They are seen in about 25% to 35% of all AML patients at diagnosis. The incidence is slightly higher in younger AML as compared to elderly AML. A FLT3 mutation has been shown to be associated with an adverse outcome due to a high relapse rate as well as poor overall survival. Over the last 14 to 15 years, a number of drugs called FLT3 inhibitors have entered the therapy arena for AML. One of the first of these was a drug called sorafenib, which is a multikinase inhibitor that, in addition to inhibiting FLT3, also inhibits other pathways such as VEGF, Raf, Ras, and others. The sorafenib as a single agent had modest activity in relapsed FLT3 mutated acute myeloid leukemia in a phase 1 trial. However, when sorafenib was combined with either induction chemotherapy such as idarubicin and cytarabine, or with hypomethylating therapy such as azacitidine, it significantly improved both the response rate and the survival in FLT3 mutated AML patients. We at MD Anderson have been using sorafenib in combination with either induction chemotherapy such as idarubicin and cytarabine, CLIA, or in combination with a hypomethylating therapy such as azacitidine for the last 8 to 10 years, and have seen improvements in survival as compared to the survival we were seeing before the use of sorafenib in FLT3 mutated patients.

However, more data has emerged with another FLT3 inhibitor called midostaurin, which is very similar to sorafenib. It is a multikinase inhibitor, and in addition to inhibiting FLT3, it inhibits other kinases. Midostaurin as a single agent in relapsed AML had response rates of about 5% to 10%. This was not very encouraging and hence it was evaluated as a combination strategy. In a phase 2 study completed in 2005, in the front-line setting, midostaurin added to induction chemotherapy showed promising results with high response rates of 70% to 80% in improved survival. This led to the development of a large multicenter, multinational phase 3 randomized study called the RATIFY study. The RATIFY study took patients below the age of 65 years of age

with FLT3 mutated acute myeloid leukemia and randomized them to receive either 3+7 induction alone (considered standard of care treatment for those patients), or 3+7 induction in combination with midostaurin. The midostaurin was given during induction on days 8 through 21, then was given during consolidation during days 8 through 21 of each consolidation, and then was given as maintenance for up to one year. In the other arm, patients would receive a placebo instead of the midostaurin, and the study was blinded. The overall endpoint of the study was survival, and the study that was presented 2016 ASH meeting met its primary endpoint with a significant improvement in the median overall survival, as well as the 5-year overall survival. Based on this, midostaurin has now been approved to be added to induction chemotherapy in patients below 65 years of age with FLT3 mutated acute myeloid leukemia. Now, why is this so important? First, it is important therapeutically because we now can improve both response rates as well as survival in FLT3 mutated patients by doing a simple intervention such as adding a FLT3 inhibitor to induction. Secondly, it also brings these molecular mutations into a clinical arena where these are no longer research-based tests. I think it is important that every new AML patient be tested at baseline for FLT3 mutations because it could actually change the treatment approach for that patient.

In the community, we recommend testing all new AML patients for FLT3 mutations, which can sometimes take 7 to 10 to 14 days to get back. Meanwhile, one may start with the 3+7 induction. When the test results are available, if the patient is FLT3 positive then we can add the FLT3 inhibitor midostaurin which can be commercially acquired through standard insurance.

There are two other FLT3 inhibitors, but I won't go into great detail on them. These are called quizartinib and gilteritinib. Both of these actually have completed their phase 3 studies. They had a very similar study design where they gave patients with FLT3 mutated relapsed AML and single-agent quizartinib versus investigator choice and/or single-agent gilteritinib versus investigator choice. What is really exciting about these agents is that as a single agent in prior phase 2 studies (200+ patients in both studies), the bone marrow remission rates were up to 50% to 55%. Now if we compare this to sorafenib and midostaurin where the bone marrow remission rates were 5% to 10%, when we started seeing 50% remission rates, we were quite encouraged. We believe that one or both of these drugs will hopefully meet the primary endpoint of response and survival in the phase 3 studies that were completed, and we should have the data on both of these by later this year and hopefully subsequent approvals of these in the future.

Now, the other tyrosine kinase inhibitors that are not as well developed as FLT3 in the acute myeloid leukemia space are tyrosine kinase inhibitors that target other mutations, such as the Philadelphia chromosome mutation. The Philadelphia chromosome mutation is a common mutation in CML and in ALL, and we rarely see this in acute myeloid leukemia or in blast phase CML. There are a number of tyrosine kinase inhibitors such as dasatinib, nilotinib and imatinib that target this pathway, and are usually used in combination with induction chemotherapy. Another group of targeted therapies that is of importance after FLT3 and the BCR-ABL targeted

therapies are the IDH inhibitors. These are more epigenetic-based therapies rather than true targeted therapies because they actually block the production of an enzyme, rather than a mutation in a receptor. Single-agent IDH inhibitor therapy has shown response rates of about 35% to 40% in multiply-relapsed acute myeloid leukemia harboring either an IDH2 mutation or an IDH1 mutation. The drug that is approved is the IDH inhibitor enasidenib which is now commercially available for relapsed acute myeloid leukemia with an IDH2 mutation. The other drug is the IDH1 inhibitor called ivosidenib and this one is currently under FDA review, and we expect that in the next two to three months, this will also become commercially available. This is another area where the testing of mutations is no longer research practice, it should become clinical standard. If you have an AML patient, either newly diagnosed or relapsed, we recommend community physicians to check for IDH1 and IDH2 mutations because this may give you a new therapeutic approach for your patients. Checking for FLT3 and IDH mutations should be standard for all AML because it will impact standard of care.