ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Midostaurin for Patients With Acute Myeloid Leukemia and *FLT3* Mutations

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H&O What is the role of FLT3 in normal cells and acute myeloid leukemia?

ML FLT3 is a receptor tyrosine kinase. The name stands for FMS-like tyrosine kinase 3. FLT3 is present in select tissues in the body. If *FLT3* function were shut down, or if the gene were completely missing from someone, it seems unlikely that there would be any major problems other than perhaps some mild immunologic defects, at least based on mouse data. When the *FLT3* gene is knocked out of a mouse, you still have a mouse. *FLT3* does, however, play a specific role in normal cells. *FLT3* drives the growth of early progenitor cells. It becomes activated in very early progenitor cells, and these cells proliferate at the early stage before they mature into neutrophils. The FLT3 receptor is expressed in most blasts, which are the malignant cells of acute myeloid leukemia (AML). An AML cell resembles a primitive progenitor cell of the myeloid series, and therefore it makes sense that *FLT3* is driving proliferation in these cells. Normally, the *FLT3* gene is activated very specifically through expression; it is a cytokine receptor, so it binds to a growth factor called the FLT3 ligand. The ligand is normally produced to generate new myeloid cell production in the normal bone marrow.

The *FLT3* mutation is the most common mutation in AML, impacting approximately 30% of patients. There are 2 types of mutations in the *FLT3* gene that render it permanently activated. The most common one is called the FLT3 internal tandem duplication (ITD) mutation, which is an inserted coding sequence, located in a specific area of the receptor that normally is responsible for keeping the gene off in a controlled fashion. When this coding sequence is disrupted, it alters the natural suppression of the receptor and the gene is free to stay active. The *FLT3*-ITD mutation occurs in 20% to 25% of patients with AML. The less common mutation is called the *FLT3* tyrosine kinase domain (TKD) mutation. This mutation occurs in approximately 7% of patients with AML, and it also constitutively activates the receptor, although by a different mechanism.

H&O What are the implications of the *FLT3* mutations on the disease course?

ML *FLT3* is a driver of proliferation, and therefore a patient who has a *FLT3* mutation has extraordinarily proliferative disease. These patients have very high white blood cell counts and often look ill. In general, having a large burden of leukemia at diagnosis is a bad sign. In certain contexts, the *FLT3*-ITD mutation is associated with a poor prognosis, or it was until we started to learn how to manage these patients. The *FLT3*-TKD mutation is associated with a somewhat better prognosis. The impact of any mutation in AML depends on the other mutations that are present. The *FLT3* mutation most commonly occurs with the nucleophosmin 1 (*NPM1*) mutation. The *NPM1* mutation modifies the effect of the *FLT3* mutation, and the prognosis is better when these mutations occur together than when the *FLT3* mutation occurs alone. It is possible to cure a patient

with both *NPM1* and *FLT3*-ITD mutations, especially if he or she is younger. A patient with just the *FLT3*-ITD mutation, particularly if it is present in most of the leukemia cells, typically has a poor prognosis, even with current therapy.

H&O What is the process for identifying *FLT3* mutations in patients with AML?

ML The polymerase chain reaction assay has been used to test for mutations for the past 20 years. Results come back quickly, in a few days. Newer assays that use next-generation sequencing do not effectively identify the *FLT3*-ITD mutation. This is a point of confusion. Physicians may be unaware that the newer assays do not detect the *FLT3*-ITD mutation, which is one of the most important mutations in AML.

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H&O What type of drug is midostaurin?

ML Midostaurin (Rydapt, Novartis) is the first FLT3 tyrosine kinase inhibitor (TKI) to emerge as an approved drug. It is a type 1 TKI. Type 1 inhibitors resemble a substrate of the kinase reaction, which is ATP. Midostaurin resembles ATP, in that it binds to the ATP binding site. Midostaurin has several targets. It was originally developed as a protein kinase C inhibitor, which was not useful for treatment. It was found that midostaurin also inhibits FLT3, and it is a first-generation FLT3 inhibitor. It is less potent and less selective than other FLT3 inhibitors. There are several newer-generation FLT3 inhibitors in development.

H&O What do clinical trials of midostaurin show?

ML In the field of AML, the gold standard for demonstrating benefit from a drug is an improvement in overall survival. In AML, studies tend to not use other endpoints, such as response rates and tumor shrinkage, that are seen in other branches of oncology. In AML, studies usually evaluate whether an investigational treatment improves 5-year survival compared with standard therapy. A phase 3 trial treated patients with conventional chemotherapy plus either midostaurin or placebo. At the end of several years of follow-up, overall survival improved by approximately 7% among the patients who received midostaurin. This trial led the US Food and Drug Administration to approve midostaurin for the treatment of adult patients with newly diagnosed AML who have the *FLT3* mutation. Midostaurin is approved for use in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

H&O Which types of patients with AML are candidates for midostaurin?

ML Any newly diagnosed patient with a FLT3-activating mutation—either *FLT3*-ITD or *FLT3*-TKD—will benefit from midostaurin added to chemotherapy. By itself, midostaurin has little activity, and it has no role as a single agent. It is also not useful for patients with relapsed disease. The role of midostaurin is therefore reserved for a select group of patients.

H&O What types of adverse events are seen with midostaurin?

ML The most common adverse events are favorable compared with other agents in oncology. An unusual characteristic is that the pills have a distinctive bad smell. Midostaurin causes nausea, but most patients are already receiving antiemetic agents for their chemotherapy.

A more important issue is the rare toxicities that can develop. These events are varied, and include pulmonary toxicity. As the use of midostaurin becomes more widespread, postapproval studies will likely identify other uncommon toxicities. Overall, however, midostaurin is remarkably well-tolerated.

H&O Do you anticipate that the treatment of AML patients with *FLT3* mutations will evolve?

ML There are many other FLT3 inhibitors coming down the pike. Gilteritinib (Xospata, Astellas) was recently approved in the relapsed/refractory setting. A randomized trial is comparing gilteritinib vs midostaurin in newly diagnosed patients. The FLT3 inhibitor quizartinib will hopefully be approved this year for relapsed/refractory patients. Quizartinib will also be studied as up-front therapy in newly diagnosed patients.

The role of FLT3 inhibitors in maintenance therapy is still under investigation. One question is whether a

patient who is in remission after receiving all treatment options can continue treatment with a FLT3 inhibitor, and if so, for how long. Will patients benefit from maintenance therapy? Treatment with FLT3 inhibitors will likely evolve over the next 5 to 10 years.

> At the end of several years of follow-up, overall survival improved by approximately 7% among the patients who received midostaurin.

H&O Does the targeting of *FLT3* mutations in AML have implications for other types of leukemia?

ML Development of the FLT3 inhibitors represents a prototype of targeted therapy. FLT3 was one of the earliest targets identified in AML, but it took some time to find drugs that target this mutation. The advent of the FLT3 inhibitors, along with the isocitrate dehydrogenase (IDH) inhibitors, showed that it was possible to identify mutations and target them. A common type of response is seen when this block in differentiation is overcome and the cells are forced to mature. The development of these drugs can provide a model for targeting other mutations.

Disclosure

Dr Levis has laboratory research agreements with Novartis, Astellas, and Fujifilm. He is a member of the advisory boards of Novartis, Astellas, Fujifilm, Daiichi Sankyo, Agios, and Amgen.

Suggested Readings

Das M. Midostaurin in *FLT3*-mutated acute myeloid leukaemia. *Lancet Oncol*. 2017;18(8):e439. doi:10.1016/S1470-2045(17)30506-5.

DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in *IDH1*-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398.

Kayser S, Levis MJ, Schlenk RF. Midostaurin treatment in *FLT3*-mutated acute myeloid leukemia and systemic mastocytosis. *Expert Rev Clin Pharmacol*. 2017;10(11):1177-1189.

Levis M. Midostaurin approved for *FLT3*-mutated AML. *Blood*. 2017;129 (26):3403-3406.

Sexauer AN, Tasian SK. Targeting FLT3 signaling in childhood acute myeloid leukemia. *Front Pediatr*. 2017;5:248. doi:10.3389/fped.2017.00248.

Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a *FLT3* mutation. *N Engl J Med*. 2017;377(5): 454-464.