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FLT3 Inhibitors in Acute Myeloid Leukemia: Increasing Options

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H&O What are the current treatments for acute myeloid leukemia (AML)?

TK In the past 5 years, the US Food and Drug Administration (FDA) has approved multiple new treatments for AML. The CD33 monoclonal antibody gemtuzumab ozogamicin (Mylotarg, Pfizer) was "re-approved." Two FLT3 inhibitors were approved: midostaurin (Rydapt, Novartis) in the frontline setting in combination with chemotherapy, and gilteritinib (Xospata, Astellas) in the relapsed/refractory setting as a single agent. There are 2 isocitrate dehydrogenase (IDH) inhibitors approved for AML: the IDH2 inhibitor enasidenib (Idhifa, Bristol Myers Squibb/Agios) and the IDH1 inhibitor ivosidenib (Tibsovo, Agios). Other recent approvals include the hedgehog inhibitor glasdegib (Daurismo, Pfizer) and a liposomal formulation of daunorubicin and cytarabine (Vyxeos, Jazz Pharmaceuticals).

There are also new oral formulations of existing parenteral drugs. Oral azacitidine, also known as CC-486 (Onureg, Celgene/Bristol Myers Squibb), was approved in the maintenance setting, and an oral formulation of decitabine and cedazuridine (Inqovi, Taiho Oncology) was approved for myelodysplastic syndrome. The most impactful drug recently approved for AML is venetoclax (Venclexta, AbbVie/Genentech), a BCL2 inhibitor. Venetoclax was first approved for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma. The drug was then found to have significant activity when combined with chemotherapy in patients with AML.

The treatment of AML has shifted from a one-size-fits-all approach, in which all patients received the same therapy, to a very targeted strategy. Younger and fit patients tend to receive intensive chemotherapy with appropriate targeted therapy, if indicated, and older or unfit patients have newer lower-intensity approaches. There are now several different subtypes of AML recognized, which are categorized phenotypically and genotypically. Genomic testing is performed prior to treatment selection. Patients who have the *FLT3* mutation receive a FLT3 inhibitor. Patients with the *IDH1* or *IDH2* mutation might receive an IDH inhibitor–based therapy combined with chemotherapy in a clinical trial. Many patients with AML are older and unfit, and therefore they may not be ideal candidates to receive intensive chemotherapy. These patients are now eligible for treatment with a hypomethylating agent (HMA) combined with venetoclax. This combination has led to response rates of approximately 65%, whereas response rates with previous treatments ranged from 20% to 30%. More importantly, the combination has profoundly improved the survival of these patients. The median overall survival was 8 months with standard HMAs but can now reach 17 months with an HMA plus venetoclax. This regimen represents a dramatic advance in AML, particularly in the older patient population.

An important insight gained from recent research is the recognition that AML is a heterogeneous disease that should be treated with specific targeted therapy when appropriate. A patient's treatment strategy must constantly evolve throughout the course of the disease.

H&O What is the role of the *FLT3* gene in AML?

TK The *FLT3* gene encodes a receptor tyrosine kinase that is strongly expressed on hematopoietic cells, particularly those of the myeloid lineage. The receptor tyrosine

kinase is stimulated by the FLT3 ligand, which is present in the microenvironment. In certain subsets of AML, the *FLT3* gene becomes mutated. There are 2 major types of mutations. One is called the internal tandem duplication (ITD). The second type, known as a point mutation, is most commonly situated at the activation loop residue D835 and occurs in the kinase domain. *FLT3* mutations are present in approximately 30% of patients with newly diagnosed AML. The mutations are more common in younger patients and in those with a normal karyotype. Approximately 80% of patients with *FLT3* mutations have the *ITD* mutation, and about 20% have the D835 mutation. A handful of patients have both mutations.

Biologic evaluations have shown that mutations in the *FLT3* gene lead to constitutive activation of the FLT3 receptor tyrosine kinase. Normally, the FLT3 ligand stimulates the FLT3 receptor, and conveys a growth signal to the hematopoietic cell, allowing it to grow, divide, and proliferate. The mutation in the *FLT3* gene confers a constitutive signal that acts without the FLT3 ligand. An analogy is that the switch is left in the "on" position. There is a constant signal for growth and proliferation of leukemic blasts. Most patients with *FLT3*-mutated AML have a high white blood cell count and proliferative disease. These clinical observations support the idea that the phenotype is derived from the constitutive activation of the receptor tyrosine kinase.

Patients with *FLT3*-mutated AML tend to have a worse prognosis than patients with *FLT3* wild-type disease. *FLT3*-mutated disease tends to be more proliferative. These patients respond to chemotherapy just as well as patients with wild-type disease, but they have a very high rate of relapse. In almost all patients with *FLT3*-mutated disease, the complete response is of a short duration, which leads to a shorter overall survival. The implication is that patients who are *FLT3*-mutated tend to have more aggressive, high-risk disease. Treatment aims to achieve a first remission so that the patient can undergo allogeneic stem cell transplant. The field is evolving, however. With the introduction of FLT3 inhibitors, it is possible to potentially "neutralize" the adverse prognosis associated with *FLT3* mutations. There are several new approaches involving the FLT3 inhibitors.

H&O What are some differences among the FLT3 inhibitors?

TK There are 2 major types of FLT3 inhibitors: type 2 and type 1. The type 2 inhibitors effectively inhibit the *FLT3* ITD mutation. They can stop the constitutive signaling associated with that mutation. However, they do not inhibit point mutations, such as the D835 mutation in the kinase domain. Patients who receive type 2 inhibitors tend to have a good initial response, but are at risk of developing a resistance mutation within *FLT3* (eg, the D835 point mutation). Sorafenib (Nexavar, Bayer) is a multikinase inhibitor that exerts activity on FLT3 as a type 2 inhibitor. Type 1 inhibitors are able to inhibit the FLT3 proteins that have a *FLT3* ITD, as well as those with a point mutation in the kinase domain, such as D835.

H&O Which FLT3 inhibitors are approved in AML?

TK Currently, 2 FLT3 inhibitors are approved in AML. Midostaurin and gilteritinib, the inhibitors that are currently approved for AML, are both type 1 inhibitors. They can inhibit the ITD conformation, as well as the D835 conformation. The approval of midostaurin was based on data from the randomized phase 3 RATIFY trial, which evaluated the addition of midostaurin to 7-plus-3 chemotherapy in patients with newly diagnosed *FLT3*-mutated AML. Midostaurin was administered during induction, as well as during consolidation. Although the response rates were similar between the 2 arms, there was a significant benefit in overall survival among patients treated with midostaurin. This trial established midostaurin in combination with chemotherapy as the standard of care for patients with newly diagnosed *FLT3*-mutated AML. Midostaurin is fairly well tolerated; it is associated with some gastrointestinal toxicity. This agent is not the most potent of the FLT3 inhibitors, but it has demonstrated a benefit in overall survival. As the new generation of FLT3 inhibitors develop, there may be some changes in the frontline approaches.

Gilteritinib is a second- or third-generation type 1 FLT3 inhibitor. This agent inhibits both the ITD and the D835 conformation. Gilteritinib has been studied in many early-phase trials and in various settings. The randomized phase 3 ADMIRAL trial evaluated gilteritinib in patients with relapsed or refractory *FLT3*-mutated AML. The patients were randomly assigned to single-agent gilteritinib or salvage chemotherapy of the investigator's choice. There was a significant survival benefit for patients who received gilteritinib vs salvage chemotherapy, leading to the approval of this agent in the relapsed/refractory setting. Gilteritinib is much more potent than midostaurin. This drug was well tolerated. Notable toxicities included elevated liver enzymes, which were not limiting.

H&O What information has been gained by the clinical use of FLT3 inhibitors in AML?

TK In almost all clinical trials, FLT3 inhibitors alone or in combination with chemotherapy improved overall survival vs standard therapy. Midostaurin in the frontline setting and gilteritinib in the relapsed/refractory setting have expanded treatment options and improved outcomes in patients with the *FLT3* mutation. These agents have

improved prognosis so much that, based on the expected risk of stem cell transplant in individual patients, clinicians might choose to forgo transplant at first remission and instead continue long-term treatment with a FLT3 inhibitor, often as a single agent.

FLT3 inhibitors are also used after transplant. In the ADMIRAL trial, a survival benefit was seen in patients who continued treatment with gilteritinib after transplant. Several phase 3 trials are evaluating FLT3 inhibitors after allogeneic stem cell transplant in patients with *FLT3*-mutated AML, including the RADIUS trial of midostaurin and the Blood and Marrow Transplant Clinical Trials Network Protocol 1506 trial of gilteritinib. The SORMAIN trial evaluated sorafenib after transplant in patients with AML with the *FLT3*-ITD mutation. Sorafenib improved relapse-free survival and overall survival, although the trial was not powered to assess overall survival.

H&O Why are newer FLT3 inhibitors needed?

TK Although the currently approved FLT3 inhibitors are effective, patients can still relapse after treatment. Resistance has been reported in both the frontline and salvage settings. New FLT3 inhibitors are needed to overcome these mechanisms of resistance. Some of these mechanisms include the development of kinase domain mutations among patients treated with type 1 inhibitors. In these cases, a second- or third-generation FLT3 inhibitor might inhibit the kinase domain. There are other kinases and other mutations that may engender resistance in that setting. In the future, there will be more potent, specific FLT3 inhibitors that can overcome some of the resistance. Recent research has suggested that newer FLT3 multikinase inhibitors may be able to inhibit other redundant kinase signaling pathways that might act as resistance mechanisms in patients with a *FLT3* mutation.

H&O Are there FLT3 inhibitors in development?

TK Several FLT3 inhibitors are in development. Quizartinib is a second- or third-generation FLT3 inhibitor. It is a type 2 inhibitor, and therefore highly specific for the ITD. It does not inhibit the D835 mutation or other activating point mutations in the kinase domain. Quizartinib was designed to be very specific for FLT3 to help reduce off-target effects. One of the reasons why tyrosine kinase inhibitors must be switched is that many of these agents have off-target effects; they inhibit other kinases in addition to FLT3. Inhibition of other kinases leads to toxicities. Quizartinib very potently inhibits FLT3, and it has much less off-target toxicity than other agents. It is associated with QT prolongation, and it can prolong cytopenias. In the phase 3 QuANTUM-R study of patients with relapsed/refractory AML, quizartinib was associated with a survival benefit vs the investigator's choice of preselected chemotherapy. However, the data alone were not yet compelling for FDA approval in relapsed/refractory AML. The ongoing QuANTUM-First trial is evaluating the addition of quizartinib to 7-plus-3 chemotherapy in the frontline setting.

Crenolanib is a type 1 FLT3 inhibitor that inhibits both the D835 mutation and the ITD mutation. An ongoing phase 3 study is comparing crenolanib vs midostaurin, both administered with cytarabine and daunorubicin, after induction chemotherapy and consolidation therapy in the frontline setting. The study is accruing slowly. Hopefully, data will be available in the next few years.

There are several phase 1/2 trials of small molecules that are FLT3 inhibitors. The small molecules CG-806, which has FLT3 inhibitor capacity, and HM-43239 are being studied in patients who developed progressive disease after receiving the other available FLT3 inhibitors. There are many FLT3 inhibitors under investigation. They differ from the available FLT3 inhibitors in terms of their toxicity profiles, higher specificities, and ability to inhibit mutations that are resistant to the approved agents.

H&O Are FLT3 inhibitors used in combinations?

TK FLT3 inhibitors appear to be most effective when used in combination regimens. One example is the use of midostaurin with 7-plus-3 chemotherapy. At my institution, we have performed several studies with intensive chemotherapy using high-dose cytarabine, idarubicin, and cladribine in combination with sorafenib or gilteritinib in the frontline setting in younger patients. These regimens were associated with dramatic response rates of 95% to 100%, with excellent long-term overall survival. Other investigators have studied FLT3 inhibitors with lower-intensity chemotherapy, such as 5-azacitidine. Our group has done work with 5-azacitidine and sorafenib, and more recently with 5-azacitidine and quizartinib. We are also performing studies with HMAs and gilteritinib.

The large, randomized phase 3 LACEWING trial evaluated the addition of gilteritinib to 5-azacitidine in newly diagnosed older patients unfit for intensive chemotherapy in the frontline setting. Unfortunately, the trial did not meet its primary endpoint of improved overall survival. Investigators are looking at strategies that combine lower-intensity therapy with FLT3 inhibitors. Data are beginning to suggest that low-intensity therapy, such as 5-azacitidine, may not be the ideal backbone to use in combination with FLT3 inhibitors, even for older patients. New backbones under investigation include cladribine plus low-dose cytarabine, which is being combined with FLT3 inhibitors in the frontline setting for older patients. This regimen is better tolerated, and the addition of cytarabine to the FLT3 inhibitor may be synergistic.

Studies at my institution are combining FLT3 inhibitors with other targeted therapy. We have a study combining venetoclax with gilteritinib or quizartinib.

The next stage is to evaluate a triplet regimen, such as a backbone of an HMA with venetoclax plus a FLT3 inhibitor. Studies are evaluating 5-azacitidine, venetoclax, and gilteritinib, as well as decitabine, venetoclax, and quizartinib. There are many different combinations with promising results. There is proven synergy between chemotherapy and FLT3 inhibitors, as well as between venetoclax and FLT3 inhibitors. We need a better understanding of the toxicity profile of these treatments, as well as how to best deliver them in a safe, effective manner.

H&O What questions remain?

TK The combination of an HMA and venetoclax has essentially become the new standard frontline therapy in older, unfit patients with newly diagnosed AML. The next pressing question concerns the ideal therapy for older and unfit patients with *FLT3*-mutated AML. Now that we have some clarity from the LACEWING trial of an HMA plus gilteritinib, the question is whether a "triplet" combination of an HMA, venetoclax, and a FLT3 inhibitor is safe and effective. There are several questions about the best use of these drugs. It is not known whether they should be administered simultaneously or sequentially. For example, in newly diagnosed unfit patients with *FLT3*-mutated AML, can one start with an HMA plus venetoclax to achieve remission, and then follow with an HMA plus a FLT3 inhibitor as longer-term maintenance? This strategy might be more tolerable than the triplet regimen. Another question concerns the frequency of dosing. For example, should venetoclax and the FLT3 inhibitor be given for the full 4 weeks during cycle 1 induction? Or should the doses be staggered or decreased? There are many aspects under study to optimize administration of FLT3 inhibitors.

Ongoing research is evaluating the mechanisms of resistance. There are patients who eventually develop resistance to the FLT3 inhibitors. A large part of this resistance can be attributed to clones that do not have a *FLT3* mutation, so it raises a separate challenge. There are also patients who have persistent *FLT3* mutations, with additional mutations in parallel that appear to provide mechanisms of resistance. There are questions regarding the patterns of relapse and how to target them effectively.

Investigators are developing new compounds in the phase 1 setting. These new compounds can be associated with co-mutations that impact prognosis.

Monitoring for minimal residual disease (MRD) is another important area of research. The traditional approach to assessment of MRD has been with flow cytometry. With new molecular methods, however, it is necessary to develop more sensitive sequencing methods that can detect any residual clones of *FLT3*-mutated AML, either at diagnosis or at the time of relapse. This information can help guide selection of the next therapy.

Disclosure

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Suggested Readings

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