

ADVANCES IN LLM

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

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Quizartinib in Acute Myeloid Leukemia



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H&O What are *FLT3-ITD* mutations, and how do they affect patients with acute myeloid leukemia (AML)?

ML An *FLT3-ITD* mutation occurs in the *FLT3* receptor protein found on the cell surface of hematopoietic cells. AML is a rapidly proliferating cancer. Internal tandem duplication of the *FLT3* gene occurs in up to one-third of patients with AML and is associated with more aggressive disease and failure of standard treatment. The therapeutic approach for these patients has traditionally included intensive induction chemotherapy, followed by consolidative chemotherapy or hematopoietic cell transplantation. We specifically refer to such patients as *FLT3-ITD* patients because they have a unique clinical presentation. AML can present in a variety of ways, but one of the more dramatic ways is that patients will have a very high white blood cell count. Furthermore, although *FLT3-ITD* patients can achieve remission with conventional chemotherapy, a large fraction of these patients relapse, and they relapse more rapidly than other AML patients who lack such mutations. *FLT3-ITD* patients have a clinical course that is almost always fatal at relapse, as the disease becomes difficult to control.

What emerges at relapse is typically an even more aggressive leukemia that becomes driven by the *FLT3* mutation. The *FLT3* receptor is supposed to function only in hematopoietic stem cells, turning on when it is time to replenish a subpopulation, and then turning off once that has been achieved. However, when there is a mutation in *FLT3*, it is permanently on. In the relapse setting in AML

patients with *FLT3-ITD* mutations, that mutant receptor is driving the cell to divide, and it provides a resistance to chemotherapy as well.

By the same token, the leukemia cell is rather addicted to that oncoprotein. Genome-wide sequencing studies of diagnostic and relapsed AML samples suggest that at presentation, an AML cell population consists of several clonal subtypes that share a common mutational ancestry but have unique complements of initiating mutations. At relapse, a dominant clone is more likely to emerge, resulting in an *FLT3*-addicted clone dominating the leukemia cell population. Therefore, the logical approach is to try to inhibit *FLT3*.

H&O What are some drugs that have been developed recently, and what are the main problems?

ML Small molecule tyrosine kinase inhibitors (TKIs) are being routinely used in the management of many malignancies, including chronic myeloid leukemia (CML), Philadelphia chromosome-positive acute lymphoblastic leukemia, gastrointestinal stromal tumors, non-small cell lung cancer, renal cell carcinoma, hepatocellular carcinoma, and sarcoma. This is the fastest growing group of drugs to receive approvals from the US Food and Drug Administration (FDA) in the last couple of years. At least 18 TKIs have been approved by the FDA for the treatment of different malignancies. Thus, it is technically possible to design a drug that will inhibit a receptor tyrosine kinase like *FLT3*. For the last several years, we have been testing different drugs for their ability to inhibit *FLT3*.

One problem with these drugs is that there are many receptor tyrosine kinases in any given cell and organism, and they are all vaguely related. When a drug is designed to inhibit 1 kinase, it often will inhibit other kinases, particularly related kinases, and that has been a real problem with *FLT3* inhibitors. In order to truly kill the AML cell that has a *FLT3* receptor, you must thoroughly and profoundly inhibit *FLT3* for days to ensure that the cell dies. Unfortunately, if you have a drug that also partially inhibits other receptor tyrosine kinases, there will be side effects. Often, patients do not tolerate inhibition of normal kinases, and this has become a technical problem in the field. The early *FLT3* inhibitors that we started working on hit too many other kinases. When doses were sufficiently increased in order to turn off *FLT3*, too many other kinases were hit, and patients essentially turned green or experienced a lot of toxicity in general.

H&O What is quizartinib? How does quizartinib compare with other *FLT3* inhibitors?

ML The first real drug that was truly designed specifically for *FLT3* and was picked for selectivity and potency was quizartinib (Ambit Biosciences). It was originally known as AC220. After trying many other kinase inhibitors developed for other cancers that happened to inhibit *FLT3* as well, quizartinib has proven to be the most potent and selective among them by far.

Again, the patients we were interested in testing first were those who had relapsed, because their disease is very much addicted to *FLT3*. We first started testing quizartinib as a single agent in patients who had a very short life expectancy and minimal therapeutic options. The responses were pretty dramatic. In more than one-third of participants, the leukemia was completely cleared from the bone marrow. Many of these patients were then able to undergo potentially curative bone marrow transplants. Patients did not have any major toxicities from quizartinib treatment. We were well above the dose necessary to inhibit the target. One problem that did arise—a side effect that patients did not notice—was an electrocardiogram abnormality called *QT prolongation*. We lowered the dose of quizartinib in order to correct this.

What we found is that patients achieved disease control. Quizartinib was able to remove most of the leukemia to barely detectable levels. However, this is still not a cure, and we would never have expected to be able to cure a relapsed AML patient with just 1 drug. What this drug did enable us to do was to take patients to an allogeneic transplant. Thus, we were taking patients who really had no meaningful chance at cure and providing opportunities for a cure. Additionally, 33% of patients who were bridged to hematopoietic stem cell transplantation after achieving a complete remission with incomplete hema-

tologic recovery were still alive after 1 year, with multiple patients alive after more than 2 years.

Ideally, quizartinib will be used in combination with existing therapies, and in earlier-stage AML patients. If used very early on, when patients present at diagnosis, quizartinib may be able to prevent relapse from occurring in the first place. I do not think that there will be resistance problems if we administer the drug in a newly diagnosed setting. Quizartinib is not going to work by itself in a newly diagnosed patient, but what we envision is that it will work in suppressing the relapse, and hopefully prevent the emergence of that *FLT3*-addicted subset of AML in patients who are at higher risk of relapse.

We are planning to test the drug as a single agent in the relapsed setting, and we will compare it with a control arm, such as chemotherapy. However, I am most anxious to test this drug in combination with chemotherapy. The hope is to get patients into remission, take them to an allogeneic transplant as a consolidation therapy, and then keep them on the drug after transplant for some period of time. This is something that we have learned to do with drugs that inhibit *BCR-ABL* or Philadelphia chromosome-positive ALL. That disease used to be inexorably fatal before the advent of TKIs, which have made it a much more manageable disease.

H&O What were some key findings from your phase 2 trial of quizartinib?

ML We presented final results of the open-label phase 2 trial of oral quizartinib in AML patients with and without *FLT3-ITD* mutations at the 2012 American Society of Hematology meeting. In cohort 2, which included 138 patients (100 with the mutation and 38 without) who received continuous treatment with quizartinib at a fixed dose throughout 28-day cycles, the composite complete response rate was 46% for patients with *FLT3*-positive disease and 32% for patients with *FLT3*-negative disease. Nearly half of the patients were refractory to their most recent therapy, and yet they responded at a very high rate to single-agent treatment with quizartinib.

Another finding was that quizartinib was extremely well tolerated. We did not have patients discontinuing treatment owing to adverse effects. Common toxicities were nausea (38%), anemia (29%), *QT* prolongation (26%), vomiting (26%), fever (25%), diarrhea (20%), and fatigue (20%). Myelosuppression, which was possibly related to *KIT* inhibition, was manageable. Thirdly, we had a very large fraction of patients bridged to an allogeneic transplant as a result of treatment with quizartinib. They would not have had that option without the drug. It was very clear that we were providing clinical benefits to these patients.

H&O Does this study have implications for clinical care?

ML Yes. Patients with very advanced leukemia have minimal treatment options available. If approved, quizartinib would likely be central to the treatment of patients with *FLT3-ITD* AML, both in the newly diagnosed setting and at relapse. If approved in AML, quizartinib will likely be tested in other cancer types, such as acute lymphoblastic leukemia, in which *FLT3* is sometimes mutated or over-expressed. Since quizartinib also inhibits the expression of *KIT* mutations, it may work in patients who have gastrointestinal stromal tumors as well.

H&O What are other promising areas of research?

ML Many researchers are jumping on the *FLT3* inhibitor bandwagon, and there are a number of other new agents emerging. One observation that we made concerning quizartinib was that there were occurrences of resistance mutations. The leukemia cell would suddenly reemerge in resistant fashion to the drug, and it would contain a mutation in the target gene that rendered it resistant to the drug. This finding indicates that the cancer cell cares about that gene, and that you are hitting the target, so it was expected. Although patients started developing resistance mutations, we were somewhat reassured that we were at least hitting the target correctly.

There are now *FLT3* inhibitors that are being developed that are effective against these resistance mutations. Second- and third-generation *FLT3* inhibitors are in development. In addition, we are looking at combining *FLT3* inhibitors with other targeted agents. Right now, the most promising area is combining these inhibitors with DNA methyltransferases, such as 5-azacytidine and

decitabine. Several ongoing trials are combining quizartinib and other *FLT3* inhibitors with these agents.

H&O What are the biggest remaining challenges for the future?

ML I think that we still have to convince the FDA that this is a drug that should be approved. Any leukemia doctor who uses quizartinib on their patients is wondering why we do not have this drug approved yet, because it is clearly clinically effective and can be used to help patients. The problem is that there is a certain rigidity in the drug approval process that sets the metric as determined by chemotherapy, thus making the system poorly suited to developing a targeted agent. Because these agents work differently than chemotherapy, the responses look different as well. The FDA is having a hard time wrapping its collective mind around what these responses mean, and why taking a patient to an allogeneic transplant is a good strategy. In general, figuring out how best to incorporate these agents into existing treatment regimens for this disease is the big challenge, and that is what ongoing trials are studying right now.

Suggested Readings

Cortes JE, Perl AE, Dombret H, et al. Final results of a phase 2 open-label, monotherapy efficacy and safety study of quizartinib (AC220) in patients ≥ 60 years of age with *FLT3* ITD positive or negative relapsed/refractory acute myeloid leukemia [ASH abstract 48]. *Blood*. 2012;120(21):48.

Grunwald MR, Levis MJ. *FLT3* inhibitors for acute myeloid leukemia: a review of their efficacy and mechanisms of resistance. *Int J Hematol*. 2013;97(6):683-694.

Levis MJ, Perl AE, Dombret H, et al. Final results of a phase 2 open-label, monotherapy efficacy and safety study of quizartinib (AC220) in patients with *FLT3*-ITD positive or negative relapsed/refractory acute myeloid leukemia after second-line chemotherapy or hematopoietic stem cell transplantation [ASH abstract 673]. *Blood*. 2012;120(21):673.