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Quizartinib, the Next FLT3 Inhibitor

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H&O What are FMS-like tyrosine kinase 3 (FLT3) inhibitors, and how have they affected the treatment of patients with acute myeloid leukemia (AML)?

JC *FLT3* mutations are a common occurrence in AML, affecting about one-third of patients, and are known to have a significant adverse effect on prognosis. The most common type of *FLT3* mutation is internal tandem duplication (ITD), which is associated with the worst prognosis compared with kinase domain mutations.[1] Given the frequency and poor prognosis of these mutations, there has been a longstanding interest in developing drugs that specifically target them, as chemotherapy alone has not been effective. Thus, FLT3 inhibitors were developed as drugs that somewhat selectively inhibit FLT3 and help manage patients with these mutations.

There has been a long history of developing FLT3 inhibitors. Although some developmental drugs, such as lestaurtinib, did not demonstrate efficacy and thus did not make it to market, others such as midostaurin (Rydapt, Novartis) and gilteritinib (Xospata, Astellas) have been approved according to demonstrated efficacy in randomized clinical trials. Some others, such as quizartinib, are being tested in clinical trials and have shown promising activity. FLT3 inhibitors have been investigated both as single agents and in combination with standard chemotherapy or other agents to try to improve patient outcomes.

In short, the *FLT3*-mutated gene leads to constitutive activation of FLT3 and the rapid proliferation of leukemia cells, and FLT3 inhibitors work well by blocking this aberrant signal.

H&O What is quizartinib, and how does it work?

JC Quizartinib is a FLT3 inhibitor that belongs to the type 2 category, which means it specifically targets the inactive conformation of FLT3.[2] It is a very potent and selective inhibitor compared with other inhibitors that are currently available or in clinical trials. Type 1 inhibitors work against the active and inactive conformation of FLT3. In kinome analysis, none of the FLT3 inhibitors are purely selective, as they all inhibit other kinases. However, quizartinib is perhaps the most selective FLT3 inhibitor available to date.[3]

> A drug that can block more than 90% of FLT3 activity, such as quizartinib, is exactly what we want.

Quizartinib, formerly known as AC-220, was investigated many years ago in a phase 1 study.[4] One of the standout features of quizartinib besides its selectivity is its potency. Preclinical studies in vitro showed that it can almost completely block FLT3 activation, making it an ideal candidate for treating *FLT3*-mutated leukemia. A drug that can block more than 90% of FLT3 activity, such as quizartinib, is exactly what we want.

Quizartinib also has excellent oral bioavailability, so it is given as a pill, similar to most other FLT3 inhibitors. It has undergone a long developmental process, starting with the phase 1 study, followed by several phase 2 studies,[5,6] a randomized study as a single agent compared with standard chemotherapy in patients with refractory or relapsed AML,[13] and more recently, combination studies. Various schedules have been tested to determine the optimal activity. With its potency and selectivity, quizartinib has great potential for managing *FLT3*-mutated leukemia in various settings.

H&O How does quizartinib compare with the other FLT3 inhibitors that are approved, specifically midostaurin and gilteritinib, and those that are in development, including sorafenib and crenolanib, for the treatment of AML?

JC I have mentioned a few key elements. Quizartinib is perhaps the most selective of these inhibitors, inhibiting the fewest other kinases. It does inhibit c-KIT, for example, but it is still fairly selective.[7] Quizartinib also differs in potency compared with other drugs, such as midostaurin.[8] In clinical doses, the concentrations of quizartinib that are achieved in patients are very effective in almost completely eliminating the activated FLT3 signal, whereas midostaurin, although effective, does not achieve the same depth of inhibition. It is worth noting that the 2 currently approved drugs, midostaurin and gilteritinib,[9] are type 1 inhibitors, whereas quizartinib is a type 2 inhibitor.

In practical terms, the type 1 inhibitors work against both the kinase domain mutation (D835 mutation) and the *FLT3* ITD mutation, whereas type 2 inhibitors, like quizartinib, only work against the *FLT3* ITD mutation. In various studies, about 20% of patients treated with quizartinib lose their response owing to the emergence of the D835 mutation as a mechanism of resistance.[10]

In cases where patients already have the D835 mutation, quizartinib is not expected to work. Other drugs may work, but usually only when *FLT3* ITD is still present alongside D835. Some other drugs in development include sorafenib, which is also a type 2 inhibitor and has been used extensively, but it is not approved for *FLT3*-mutated AML. It is approved for other indications in cancer, such as renal cancer. However, it is not as selective as quizartinib.[11] Crenolanib is earlier in its development and is a type 1 inhibitor.[12] There are no published single-agent data yet, making it difficult to assess, but it is likely not as potent as quizartinib.

One interesting finding with quizartinib is that it induced responses in about 30% of patients without *FLT3* mutations. Its possible use in this setting deserves further investigation.

H&O Could you describe the phase 3 QuANTUM-R study on quizartinib, including safety, adverse events, and toxicities?

JC The QuANTUM-R study was conducted to evaluate the efficacy of single-agent quizartinib vs standard salvage chemotherapy in patients with *FLT3* ITD–mutated AML who had refractory or relapsed disease.[13] Patients were randomly assigned to receive either quizartinib or physician's choice among several standard chemotherapy regimens, which consisted of cytarabine alone; mitoxantrone, etoposide, and cytarabine (MEC); or fludarabine, cytarabine, and idarubicin (FLAG-Ida). The study showed that quizartinib led to significant improvements in overall survival, event-free survival, and response rates compared with standard chemotherapy, and had a manageable safety profile in patients with rapidly proliferative disease and very poor prognosis. These results were achieved with a single oral agent, which is remarkable considering the aggressive nature of the disease and the fact that the control arm included standard, mostly intensive chemotherapy.

In terms of the adverse events, quizartinib was well-tolerated. One notable observation was that owing to the inhibition of c-KIT, there was sometimes a delayed recovery of the neutrophils and platelets after using quizartinib, but this was not very different than with standard chemotherapy.

The most common nonhematologic grades 3 to 5 treatment-emergent adverse events for quizartinib and chemotherapy were sepsis or septic shock (19% for quizartinib, 18% for chemotherapy), pneumonia (12% vs 9%, respectively), and hypokalemia (12% vs 9%, respectively).

One of the concerns with quizartinib is QTc prolongation. This effect was observed in patients throughout the drug's development, but fortunately, grade 3 QTc prolongation was rare, and serious complications such as torsades de pointes and other severe arrhythmias were not seen. This suggests that the drug was well-tolerated and more effective than standard chemotherapy in this setting, confirming what we had assumed from phase 2 studies.

The results supported the benefit of quizartinib in this patient population, and the study met its primary endpoint. However, there were some issues that were questioned by the regulatory authorities in terms of the design of the study and some definitions that prevented the drug from being approved.

H&O Have any other studies investigated quizartinib, and are any of those trials open right now?

JC Yes, there have been additional studies conducted, including the QuANTUM-First study, which is perhaps the most relevant one.[14] It was a randomized study that included patients with newly diagnosed AML with a *FLT3* ITD mutation. They were randomized to receive either standard chemotherapy alone or in combination with quizartinib. This study used a combination of quizartinib and chemotherapy because these were patients newly diagnosed with AML. The study showed a significant survival benefit for patients who received the combination compared with patients who received only chemotherapy.

The combination was continued through induction and consolidation, followed by continuation of therapy with quizartinib alone after the completion of consolidation. This is a very important study because it establishes the value of quizartinib in this context, as we want to include FLT3 inhibitors from the initial diagnosis in patients with *FLT3* mutations. QUANTUM-First established quizartinib as a very good treatment option for patients with newly diagnosed *FLT3*-ITD–mutated AML. It follows the same concept as midostaurin, but with a drug that, in my opinion, might have additional benefits in terms of potency.

There are other studies that are looking at quizartinib in various combinations. The focus is on combinations because in AML, it is hard to believe that a single agent, however potent and effective, can eradicate the leukemia. One interesting combination being studied is quizartinib with decitabine and the BCL2 inhibitor venetoclax.[15] Other combinations include CPX-351, which is a liposomal formulation of cytarabine and anthracycline, and other types of chemotherapies.[16] Although QuANTUM-First established the benefit of quizartinib compared with standard chemotherapy, more research is needed to optimize and improve responses and survival rates, and to find other indications for quizartinib.

The QuANTUM-First study is the pivotal study that received priority review from the US Food and Drug Administration (FDA).[17] The study was discussed with the FDA, and the positive results suggested a benefit that now needs to be fully assessed for approval. Given quizartinib's track record of efficacy in other settings, the positive results make it an attractive candidate for a rapid review. The FDA will need to review all the clinical trial data, including efficacy and safety, to ensure that it meets the criteria for approval. If it does, then it may be approved for regular use and would be a welcome addition to our armamentarium for treating patients with this high-risk subset of AML.

H&O Where are we going next with quizartinib?

JC I think the key here is to explore the potential of quizartinib in other settings. One approach is to investigate other combinations, both in the frontline and salvage settings, such as combining it with other agents, and using it as maintenance after stem cell transplant. Another important area of research is to better understand the mechanisms of resistance, including the development of new mutations. Emergence of new mutations is an issue that applies to all FLT3 inhibitors; understanding it will help us identify the best way to us quizartinib in different clinical settings. Although adding quizartinib to chemotherapy has already been shown to increase survival, there is still room for improvement. We need to find the best combination of therapies for each patient group to achieve the most optimal outcome.

H&O Is there anything else you would like to add?

JC One important thing to note is that in the past, patients with *FLT3*-mutated disease had poor outcomes, even with a transplant—which is typically the preferred approach for these patients. In fact, patients with this mutation who underwent a transplant had worse outcomes compared with those without the mutation. However, with the introduction of FLT3 inhibitors and the development of newer, more selective, and more potent inhibitors, there has been significant improvement in the treatment of *FLT3*-mutated AML. Although we may not have achieved the desired outcomes yet, this is a significant step forward for these patients.

Disclosures

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(Continued from page 230)

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Suggested Readings

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