FLT3-positive AML

Ik-Chan Song
Department of Internal Medicine, College of Medicine, Chungnam National University, Daejeon, Korea

Acute myeloid leukemia (AML) is a genetically heterogeneous disease associated with poor clinical outcomes. Mutations in *FLT3* are among the most frequently observed genetic alterations in AML. Approximately 25% of patients with newly diagnosed AML harbor *FLT3* internal tandem duplication (ITD) mutations, while an additional 7% carry point mutations in the tyrosine kinase domain (TKD). Historically, *FLT3* mutations have been associated with adverse prognosis, including a higher risk of relapse and shorter overall survival compared with *FLT3* wild-type and *FLT3*-TKD AML.

However, with the incorporation of FLT3 inhibitors into AML treatment, *FLT3*-mutated AML is now classified as an intermediate-risk group. To date, three FLT3 inhibitors have been approved by the US Food and Drug Administration: midostaurin, gilteritinib, and quizartinib. Midostaurin and quizartinib are approved for frontline treatment in combination with standard induction chemotherapy (the “7+3” regimen), whereas gilteritinib is approved for patients with relapsed or refractory AML.

Both midostaurin and quizartinib demonstrated a similar overall survival benefit, with a hazard ratio for death of 0.78, corresponding to a 22% reduction in mortality risk. Notably, the pivotal RATIFY trial of midostaurin enrolled patients younger than 60 years, whereas the QuANTUM-First trial of quizartinib included patients up to 75 years of age. In addition, midostaurin was evaluated in patients with both *FLT3*-ITD and *FLT3*-TKD mutations, while quizartinib, a type II FLT3 inhibitor, was studied exclusively in patients with *FLT3*-ITD–mutated AML.

Gilteritinib significantly improved outcomes in relapsed or refractory AML, prolonging median overall survival by approximately 4 months compared with salvage chemotherapy and reducing the risk of death by 36%. Ongoing studies are currently evaluating gilteritinib in the frontline setting, and results from phase 1/2 trials have been highly promising.

In this lecture, we review the current role of FLT3 inhibitors in AML and discuss future perspectives on the optimal integration of FLT3-targeted therapies in the evolving treatment landscape.