Triple Targeting in Myelofibrosis with Momelotinib: Integrated Therapeutic Approach via JAK1/2 and ACVR1 Inhibition

Sung-Eun Lee
Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Myelofibrosis (MF) is a clonal myeloproliferative neoplasm characterized by splenomegaly, debilitating constitutional symptoms, progressive cytopenias, and a risk of leukemic transformation. Despite advances in JAK inhibitor therapy, MF remains a clinically heterogeneous disease that can be broadly categorized into proliferative and cytopenic phenotypes. In particular, patients with cytopenic MF, often burdened by anemia and transfusion dependence, continue to face significant unmet therapeutic needs. Momelotinib is a unique oral JAK inhibitor with dual inhibition of JAK1/2 and activin A receptor type 1 (ACVR1), offering a mechanistically distinct approach that targets inflammatory signaling, splenomegaly, and anemia. This presentation reviews the clinical evidence supporting momelotinib (Omjjara), with a focus on the phase 3 SIMPLIFY-1 and MOMENTUM trials. These studies evaluated momelotinib across JAK inhibitor-naïve and JAK inhibitor-experienced MF populations, including patients with baseline anemia, and demonstrated clinically meaningful benefits in spleen volume reduction, symptom control, and anemia-related outcomes, including transfusion independence. Beyond efficacy data, this lecture emphasizes the importance of individualized JAK inhibitor selection based on clinical phenotype, baseline cytopenias, prior treatment exposure, and therapeutic goals. Practical guidance on initiating momelotinib therapy is provided, including dosing considerations, laboratory monitoring, and management of key safety watchpoints. Collectively, this integrated therapeutic approach highlights the role of momelotinib as a differentiated treatment option, particularly for patients with anemia, and underscores the need for phenotype-driven decision-making in the evolving MF treatment landscape.