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Letter to the Editor

Revumenib: the newly approved food drug administration drug for the treatment of relapsed acute leukemia with a KMT2A translocation

Sir,

On November 15, 2024, the US food and drug administration (FDA) granted approval for Revumenib for the treatment of relapsed or refractory acute leukemia in adult patients and pediatric patients aged 12 months or older who exhibit a lysine methyltransferase 2A (KMT2A) translocation.[1] This subset of acute leukemia is driven by the pathological interaction between menin proteins and the KMT2A gene, a critical epigenetic regulator. This interaction facilitates the rearrangement of KMT2A, which underpins leukemogenesis, contributing to the pathophysiology in approximately 10% of acute leukemia cases.[2]

Revumenib, commercially known as Revuforj, operates as a targeted inhibitor of the menin-KMT2A interaction. By disrupting this interaction, Revumenib downregulates the transcriptional expression of key oncogenic drivers, including the myeloid ectopic viral integration site 1 (MEIS1) gene and Homeobox (HOX) genes. The MEIS1 gene encodes a transcription factor integral to hematopoietic regulation and has a pivotal role in sustaining leukemia progression. Similarly, HOX genes, which are indispensable in embryonic development and the regulation of cellular differentiation, exhibit aberrant expression in KMT2A-rearranged leukemia, promoting uncontrolled cellular proliferation and malignant transformation.

The efficacy of Revumenib was rigorously evaluated in the AUGMENT-101 trial, an open-label, multicenter study conducted with a single-arm cohort. The trial enrolled 104 participants, including both adult and pediatric patients as young as 30 days, all of whom had relapsed or refractory acute leukemia characterized by KMT2A translocations.[3] The primary efficacy outcomes included the rates of complete remission (CR) and CR with partial hematologic recovery (CRh), the duration of CR+CRh, and the transition from transfusion dependence to independence. Among the patients, the CR+CRh rate was reported to be 21.2% (95% CI: 13.8, 30.3), with a median duration of response of 6.4 months (95% CI: 2.7, not estimable).[3] The median time to achieve CR or CRh among the 22 responding patients was 1.9 months, with a range of 0.9 to 5.6 months. Notably, among the 83 patients dependent on red blood cell (RBC) or platelet transfusions at baseline, 12 (14%) achieved transfusion independence during any 56-day post-baseline period. Additionally, of the 21 patients who were transfusion-independent at baseline, 10 (48%) maintained their independence during the same timeframe.

Revumenib's safety profile was characterized by several adverse events. Commonly reported side effects included nausea, vomiting, and febrile neutropenia. Of particular concern was the occurrence of QT interval prolongation, which necessitates careful monitoring due to its potential to precipitate serious cardiac arrhythmias.[4] Furthermore, a subset of patients developed differentiation syndrome (DS), a serious complication observed at grade 2 or lower in severity. DS presents with clinical features such as fever, arthralgia, leukocytosis, pleuro-pericardial effusion, and, in more severe cases, renal or respiratory failure.[5] The recommended dosage of Revumenib is tailored according to patient weight and the concurrent use of strong CYP3A4 inhibitors, as these factors influence drug metabolism and pharmacokinetics.

This approval marks a significant milestone in the therapeutic management of KMT2A-rearranged acute leukemia, providing a novel, targeted treatment option for a high-risk patient population with limited alternatives.

Aibannehbok E. L. Sohliya*
Department of Medicine, Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER), Puducherry, India

***Correspondence to**
Dr. Aibannehbok E. L. Sohliya,
E-mail: sohliyaaiban@gmail.com

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