Letter to the Editor

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Breakthrough treatment choice for Acute Myeloid Leukemia in pediatric and adult patients: Revumenib, an oral selective inhibitor of KMTA2Ar

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Dear Editor,

Acute myeloid leukemia (AML) represents the predominant manifestation of acute leukemia in the adult population, whereas in children, it ranks second in terms of frequency. It is characterized by genetic mutations and epigenetic dysregulation resulting in a heterogeneous population of malignant cells with blocked differentiation resulting in increased proliferation and self-renewal activity [1]. Every year 20,000 new cases of AML are diagnosed in the United States, whereas the global burden of the disease is believed to range between 119,000 to 352,000 cases per annum.[2] NPM1 gene mutations are the most encountered genetic aberrations in acute myeloid leukemia (AML), being detectable in about one-third of adult AML and 50–60% of AML patients with normal karyotype. The mutant NPM1 is directly involved in promoting increased expression of homeobox (HOX) genes, which are necessary for maintaining the leukemic cells in undifferentiated state.[3]

Recent studies have shown the importance of MLL1-Menin interaction in AML with mutated nucleophosmin 1 (NPM1c). MLL1 (also known as lysine methyltransferase 2A [KMT2A]) is located on chromosome 11q23, but chromosomal translocation (MLL1-rearrangement [MLL1-r]) is observed in 5%–10% of acute leukemia cases (AML and ALL) in adults and children. This leads to the expression of chimeric MLL1 fusion proteins (ML-FP) that drive leukemic gene expression and proliferation and prevent hematopoietic differentiation, consequently giving rise to a particularly aggressive subtype of leukemia with an unfavorable outcome.[1,4] Chromosomal rearrangements involving KMT2A gene are prevalent in neonates with acute leukemia,[5] and affects 75% of newborns with ALL.[6] Research findings suggest that this crucial molecular alternation takes place antenatally, leading to leukemia during the infantile period.[5]

Although induction therapy achieves complete remission (CR) in 60–80% cases, no targeted therapies have specifically been approved for acute leukemia with KMT2A rearrangement (KMT2Ar) or mutated NPM1currently. Unfortunately, the median survival is relatively brief at 8.5 months with 2-year and 5-year Overall Survival (OS) rates just 32% and 24%, respectively.[2] Furthermore, existing research has suggested that circRNAs are capable of playing a role in the post-transcriptional regulation of AML by binding miRNAs, activating downstream signaling cascades, and regulating the expression of related genes, closely correlated with a wide variety of processes of AML.[7] AML has a poor prognosis and a considerable tendency to relapse[1] therefore, the need for effective treatment is undeniable.

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On 5 December 2022, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy Designation (BTD) for Revumenib as a first-and best-in-class therapy for the treatment of adult and pediatric patients with relapsed or refractory (R/R) acute leukemia harboring a KMT2Ar.[8] Revumenib, previously known as SNDX-5613, is a potent, oral and selective inhibitor of the menin–KMT2A interaction. It disrupts the interaction between Menin and its binding pocket in MLL1/2 and MLL1-FP, causing differentiation and apoptosis of AML cells expressing MLL-FP or NPM1c[9] Thus, this development represents a major step forward in our efforts to combat this devastating disease and provides new hope for patients and their families.

To evaluate the safety, tolerability, pharmacokinetics, and efficacy of orally administered Revumenib, AUGMENT-101 Phase 1 open-label trial was conducted. In between 5 November 2019 and 31 March 2022, a total of 68 patients with nucleophosmin mutant and KMT2A-rearranged relapsed/refractory (R/R) acute leukemia were enrolled. The cohort included adult and pediatric patients, having a median age of 50.5 years and 2.5 years, respectively. 56 patients (82%) had relapsed or refractory AML, 11 (16%) suffered from ALL, and one with mixed-phenotype acute leukemia (2%)[10] They were allocated into two separate cohorts based on concomitant treatment of revumenib with a strong CYP3A4 inhibitor or a less potent one. Arm A enrolled 37 patients receiving between 226 mg and 276 mg of revumenib once every 12 h without a strong CYP3A4 inhibitor, while Arm B enrolled 31 patients taking 113 mg–163 mg of revumenib at the same interval but with a strong CYP3A4 inhibitor.[10,11] Revumenib has demonstrated a promising outcome in its Phase 1 open-label trial; 30% of the 18 evaluable patients among 60 total patients achieved complete remission or complete remission with partial hematologic recovery (CR/CRh), while 78% of these 18 participants attained measurable residual disease (MRD) negativity.[10]

Though Revumenib opens a new door of hope for patients and physicians, the treatment also carries risks. Differentiation syndrome is a notable treatment-related adverse event (AE) that occurred in 16% of revumenib recipients.[11] Furthermore, irregular cardiac rhythm was another notable AE, which took place in 53% of revumenib recipients.[11] Nevertheless, the medication was well-tolerated by study participants and no participants stopped taking the therapy due to treatment-related adverse effects. Thus, AUGMENT-101 may potentially serve as the basis for changing the treatment paradigm for patients with relapsed or refractory KMTA2-rearranged acute leukemia for outweighed positive outcomes.[8] Therefore, the development of Revumenib represents an important turning point in our fight against acute myeloid leukemia.

The endorsement of this drug is a laudable achievement, and it demonstrates the unwavering commitment of researchers and healthcare professionals to discovering effective treatments for such a fatal disease. In conclusion, this drug offers a ray of hope to patients and their families and also inspires researchers to continue their quest for the cure which is evident by the fact that Phase 2 pivotal portion of AUGMENT-101 is currently underway.[11] Therefore, it is crucial that we continue to support research into leukemia and the development of new treatments to envisage a time where leukemia is eradicated.

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