Exploring new horizons in menin: it's bleximenib's turn

Bradley Rockwell and Marina Konopleva

Montefiore Einstein Comprehensive Cancer Center, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

Correspondence: B. Rockwell
brockwel@montefiore.org

Received: February 18, 2025.
Accepted: March 6, 2025.
Early view: March 13, 2025.

https://doi.org/10.3324/haematol.2024.287142

Acute myeloid leukemia (AML) is a malignant neoplasm of the bone marrow with diverse genetic etiologies. For decades AML has been treated with cytotoxic chemotherapy, specifically cytarabine and anthracycline combinations. The small molecule venetoclax, an inhibitor of Bcl-2, was approved by the Food and Drug Administration (FDA) in 2018 for the treatment of AML, starting a revolution in small molecule research.

Menin, a tumor suppressor scaffolding protein, has attracted particular interest in the past few years given its well-known biology in leukemogenesis through its interaction with KMT2A, particularly in mixed lineage leukemia (MLL) and AML with *KMT2A* translocation.[1] AML with *KMT2A* rearrangement secondary to prior treatments with chemotherapy and granulocyte-monocyte progenitor-like AML are of particular concern due to their known resistance to standard cytotoxic chemotherapy.[2] Menin and its interaction with KMT2A is thought to be leukemogenic through interactions with transcription factors, the DNA damage/stress response system, as a signaling pathway modulator, and through epigenetic changes.[1] Many small molecule menin inhibitors are gradually coming onto market, such as ziftomenib and revumenib, but are still in phase I or II with no drug in phase III testing as of February 2025. Revumenib recently received FDA approval for use in relapsed and refractory AML with *KMT2A* translocation. With that, over 90% of patients in the AUGMENT-101 study experienced ≥ grade 3 treatment-associated adverse events, making off-target effects an issue.[3] In this issue of *Haematologica*, Hogeling *et al*. describe their preclinical experiments with patients' samples, which help to uncover possible mechanisms by which the drug JNJ-75276617 (bleximenib) prevents proliferation of AML cells and possibly drives differentiation, with limited effects on healthy CD34$^+$ cells.[4]

First and foremost, they showed preclinically that bleximenib is effective against *KMT2A*-rearranged and *NPM1*-mutated leukemic cells, but less toxic to healthy CD34$^+$ cells. This is consistent with the clinical data from trials on revumenib[3,5] and ziftomenib[6] showing efficacy without prolonged cytopenias. Notably, there were wildtype *KMT2A* and wildtype *NPM1* patients' samples that did respond. These included AML with mutations of *CEBPA*, a regulator of stem cell differentiation, and *NUP98*-rearranged AML. This shows possible use of menin inhibition outside of *KMT2A*-rearranged or *NPM1*-mutated AML.

Next, they set out to determine whether this effect resulted from preventing the proliferation of malignant cells or from effects on differentiation. Ultimately, it was found to be either, both, or neither. In some cells, the effect was from the prevention of proliferation and induction of differentiation. Some just from proliferation. Some just from induction of differentiation. Some from neither. This shows that we have only scratched the surface, but likely bleximenib works through multiple mechanisms.

To further characterize how the KMT2A-menin interaction causes AML through epigenetic changes, they next performed chromatin immunoprecipitation sequencing on samples from three patients. Here they found downregulation of histone modification H3K4me3 on the important transcription factor MEIS-1 and the post-transcription gene regulator IGF2BP2. While they noted heterogeneity in patients' samples, there seems to be a clear epigenetic role of menin-inhibition that requires further investigation. Not only did they discover a potential mechanism for impaired proliferation and induced differentiation, but they also suggest that menin inhibition with bleximenib causes an immunogenic response with reactivation of antigen-presenting mechanisms, specifically upregulation of MHC class I and class II expression. It is now well established that the immune system plays a key role in the development of AML. Impressively they showed that HLA expression is upregulated after treatment with bleximenib and, importantly, that this is independent of MEIS-1, a known leukemogenic hemeobox transcription factor.[7]

To augment this understanding of the immune system response, they next treated cells with bleximenib and then exposed them to activated T cells from healthy donors. Half of the samples were noted to have an increase

in sensitivity to allogeneic T cells. This should happily be expanded upon in the clinical setting, especially in cases of *KMT2A*-AML. Given that these types of AML are often secondary to previous treatments with chemotherapy and are themselves often resistant to chemotherapy, allogeneic stem cell transplantation (SCT) is an essential part of the treatment paradigm. If the preclinical response to bleximenib and allogeneic T cells is true clinically, then augmenting the graft-*versus*-leukemia effect in allogeneic SCT needs to be assessed either prior to the allogeneic transplant or as maintenance after it. T-cell activity in an autologous setting was also assessed but unfortunately, to date, autologous T-cell therapies in AML, autologous SCT and chimeric antigen receptor T-cell therapy, have been underwhelming.

Determining resistance mechanisms will be a crucial next step in the search for a successful menin inhibitor. Recent studies have suggested that loss of polycomb repressive complex 1.1 subunits, independent of the menin-MLL target, is an important mechanism of resistance. This leads to epigenetic reactivation of non-canonical targets. Interestingly, these cells are sensitive to venetoclax, showing that combination therapy may be beneficial.[8] Hogeling *et al.* note that the *MEIS* locus is downregulated by menin inhibition and mention their plans to further explore whether this is dependent on polycomb proteins. We eagerly await these future results.

In all, targeting menin shows promise through the many small molecule inhibitors that have been developed recently. While it is clear that we are still uncovering the many mechanisms by which menin inhibition works and resistance occurs, Hogeling *et al*. have laid the groundwork for future preclinical and clinic studies with bleximenib. Recently, attempts have been made to determine preclinically which patients will respond to the small molecule venetoclax with rapid *ex vivo* sensitivity testing.[9,10] Applying this same rationale to menin inhibition could help to differentiate those AML cell lines that do and do not respond in specific patients. With all the recent developments of small molecular inhibitors playing a role in the treatment of AML, it is hard to see menin inhibition not being a major player.

Disclosures

BR has no conflicts of interest to disclose. MK has received research funding from AbbVie, Allogene, AstraZeneca, Genentech, Gilead, ImmunoGen, MEI Pharma, Precision, Rafael, Sanofi and Stemline; has received advisory/consulting fees from AbbVie, AstraZeneca, Auxenion, Bakx, Boehringer, Dark Blue Therapeutics, F. Hoffman La-Roche, Genentech, Gilead, Janssen, Legend, MEI Pharma, Redona, Sanofi, Sellas, Stemline and Vincerx; holds stock options with or has received royalties from Reata Pharmaceuticals; and has patent agreements with Novartis, Eli Lilly and Reata Pharmaceuticals.

Contributions

BR wrote and edited the manuscript. MK reviewed and edited the manuscript.

References

1. Dhiman S, Dhillon V, Balasubramanian SK. Targeting menin in acute myeloid leukemia: therapeutic advances and future directions. Cancers. 2024;16(22):3743.
2. Issa GC, Zarka J, Sasaki K, et al. Predictors of outcomes in adults with acute myeloid leukemia and KMT2A rearrangements. Blood Cancer J. 2021;11(9):1-10.
3. Issa GC, Aldoss I, Thirman MJ, et al. Menin inhibition with revumenib for KMT2A-rearranged relapsed or refractory acute leukemia (AUGMENT-101). J Clin Oncol. 2025;43(1):75-84.
4. Hogeling SM, Lê DM, Rose NL, et al. Bleximenib, the novel menin-KMT2A inhibitor JNJ-75276617, impairs long-term proliferation and immune evasion in acute myeloid leukemia. Haematologica. 2025;110(6):1278-1291.
5. Issa GC, Aldoss I, DiPersio J, et al. The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. Nature. 2023;615(7954):920-924.
6. Wang ES, Issa GC, Erba HP, et al. Ziftomenib in relapsed or refractory acute myeloid leukaemia (KOMET-001): a multicentre, open-label, multi-cohort, phase 1 trial. Lancet Oncol. 2024;25(10):1310-1324.
7. Garcia-Cuellar M-P, Prinz A, Slany RK. Meis1 supports leukemogenesis through stimulation of ribosomal biogenesis and Myc. Haematologica. 2022;107(11):2601-2616.
8. Zhou X, Zhang L, Aryal S, et al. Epigenetic regulation of noncanonical menin targets modulates menin inhibitor response in acute myeloid leukemia. Blood. 2024;144(19):2018-2032.
9. Waclawiczek A, Leppä A-M, Renders S, et al. Combinatorial BCL2 family expression in acute myeloid leukemia stem cells predicts clinical response to azacitidine/venetoclax. Cancer Discov. 2023;13(6):1408-1427.
10. Kytölä S, Vänttinen I, Ruokoranta T, et al. Ex vivo venetoclax sensitivity predicts clinical response in acute myeloid leukemia in the prospective VenEx trial. Blood. 2025;145(4):409-421.