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Editorial

Introduction to a review series on small-molecule targeted therapies for lymphoid malignancies

Since the introduction of imatinib and rituximab into routine hematology practice for chronic myeloid leukemia and B-cell lymphomas, respectively, targeted therapies have become the major drivers for improved outcomes in an ever-increasing range of hematological malignancies. Targeted therapies can be small molecules, biological agents, or cellular therapies. Of these, small molecules have had arguably the greatest impact over the last 10 to 20 years, as they have transformed the treatment landscape of diseases such as multiple myeloma, chronic lymphocytic leukemia (CLL), and some lymphomas.

In particular, over the last 8 years, the treatment of patients with CLL or specific B-cell lymphomas has been advanced substantially by the introduction of potent inhibitors of intracellular pathways of importance for B-cell development, proliferation, and/or survival. This review series focuses on these drugs, all orally bioavailable: Bruton tyrosine kinase (BTK) inhibitors, such as ibrutinib; phosphoinositide 3-kinase (PI3K) inhibitors, such as idelalisib; and BH3 mimetics, such as the BCL2 inhibitor, venetoclax.

Rather than recapitulating summaries of all knowledge about these inhibitors, the reviews were invited to focus on the areas of most current scientific and clinical importance and to identify key new knowledge that should inform future exploration of their applications.

The reviews in this series include:

- Deborah M. Stephens and John C. Byrd, "Resistance to Bruton tyrosine kinase inhibitors: the Achilles heel of their success story in lymphoid malignancies"
- Wendan Xu, Philipp Berning, and Georg Lenz, "Targeting B-cell receptor and PI3K signaling in diffuse large B-cell lymphoma"
- Andrew W. Roberts, Andrew H. Wei, and David C. S. Huang, "BCL2 and MCL1 inhibitors for hematological malignancies"

The first BTK inhibitor, ibrutinib, was approved for use in late 2013 and now BTK inhibitors are central to the management of patients with CLL, relapsed mantle cell lymphoma, Waldenstrom macroglobulinemia, and marginal zone lymphoma. The first review in this series, by Byrd and Stephens, tackles the critical question as to why this highly successful class of drugs can fail through the development of secondary resistance. They explain what we know about the molecular basis for disease progression during ongoing continuous treatment of each indication, and how this may be tackled in the future. In doing so, they explore how mechanisms of resistance can vary between different B-cell malignancies and review how BTK resistance can be managed in CLL.

Among B-cell lineage malignancies, diffuse large B-cell lymphoma (DLBCL) stands out as an unfulfilled opportunity for small-molecule targeted therapies. In the second review Xu, Berning, and Lenz describe this challenge. Starting with a summary of current knowledge of how a substantial fraction of DLBCLs is addicted to oncogenic B-cell receptor and PI3K signaling caused by different stimuli and various genetic aberrations, they explore preclinical and clinical data on efficacy of small molecule inhibitors. Given the importance of PI3K signaling, they focus on the data for different available PI3K inhibitors, including copanlisib, idelalisib, and umbralisib, and describe the mechanisms of resistance that seem to be in play. Looking ahead, they speculate on how this class of drug could be incorporated into new treatment regimens.

In the final review, Roberts, Wei, and Huang bring us up-to-date with rapidly emerging clinical and translational data on the use of a totally new class of anticancer drug, BH3 mimetics. Unlike BTK inhibitors and PI3K inhibitors, BH3 mimetics do not abolish or affect enzyme (kinase) activity. Rather, they inhibit protein-to-protein interactions. These drugs are designed to mimic the action of naturally occurring proapoptotic intracellular proteins (BH3-only proteins), triggering cell death in leukemia and lymphoma targets by electively binding and preventing the function of the prominent prosurvival proteins, BCL2 or MCL1. The article highlights the unique mechanism of action and how that translates into clinical efficacy. Using the first registered BH3 mimetic, venetoclax, as the example, it explores similarities and variations in the activity of BCL2 inhibition in different types of hematological malignancies, including CLL, lymphomas, myeloma, and acute myeloid leukemia. The authors provide a useful summary of what we know about predictive biomarkers and clinically proven mechanisms of resistance, before turning their attention to the potential for inhibitors of MCL1 and what can be expected given lessons learned with venetoclax.

Collectively, these reviews bring the field up-to-date in selected applications in lymphoid malignancies, and beyond. With >20 BTK inhibitors, >15 PI3K inhibitors, 8 BCL2 inhibitors, and 5 MCL1 inhibitors in routine use or development, we can expect these small-molecule drugs to exert even greater impact on outcomes for patients in the future. We hope that these reviews are signposts for these future advances.

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