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LYMPHOID NEOPLASIA

Comment on Khaw et al, page 1382

Cotargeting BCL-2 and BCL-XL for maximal efficacy in ALL

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In this issue of Blood, Khaw et al show that in contrast to the impressive antileukemic activity achieved by sole BCL-2 inhibition in chronic lymphocytic leukemia (CLL), optimal antileukemic activity in pediatric acute lymphoblastic leukemia (ALL) xenografts required concurrent inhibition of both BCL-2 and BCL-XL.1 Venetoclax, a selective BCL-2 inhibitor, demonstrated inferior in vivo objective response of 26% as compared with an objective response of 61% with navitoclax, an inhibitor of BCL-2, BCL-XL, and BCL-W, in comparable xenograft panels of high-risk pediatric ALL.2 One important exception was the poor prognosis subgroup of pediatric mixed lineage leukemia-rearranged ALL (MLLr-ALL). Antagonism of BCL-2 alone proved efficacious in 50% of the MLLr-ALL xenografts as compared with 20% of non-MLLr-ALL xenografts. In vitro evaluation of navitoclax, venetoclax, or selective BCL-XL inhibitor (A-1155463) demonstrated that combined BCL-2 and BCL-XL inhibition by navitoclax was more potent than isolated inhibition of either pathway alone by venetoclax or by selective BCL-XL inhibitor A-1155463, respectively, across a broad range of B-cell ALL (B-ALL) and T-cell ALL (T-ALL) xenografts. There was a significant correlation between the responses of individual xenografts to navitoclax and venetoclax, but not A-1155463, suggesting that BCL-2 inhibition is of central importance, but on its own insufficient to induce maximal antileukemia activity in pediatric ALL.

Pediatric B-ALL is a heterogeneous disease with varying outcomes based on molecular subtype, age, white blood cell count at diagnosis, cytogenetics, day 14 bone marrow response, and post-induction minimal residual disease status. In the last decade, there has been significant progress in the therapy of patients with ALL, with encouraging clinical activity demonstrated by monoclonal antibodies (mAbs) and chimeric antigen receptor (CAR) T cells. mAbs target highly expressed “leukemia” surface antigens and include (1) naked antibodies against common lymphoid markers such as anti-CD22 (epratuzumab), (2) antibody–drug conjugates linked to a highly potent toxin such as calicheamicin (inotuzumab ozogamicin), or (3) bispecific T-cell engaging agents that recruit and promote proximity induced cytotoxicity of tumor cells by T cells (blinatumomab).3,4 CAR T cells targeting CD19 have produced dramatic responses in heavily pretreated B-ALL patients. In spite of these breakthroughs, a fraction of children will be primary refractory or lose response to antigen-targeted immunologic therapies by target
The study by Khaw et al suggests that unlike CLL, the inhibition of BCL-2 alone may not produce significant and durable responses in pediatric ALL. One possible explanation for the differential sensitivity to isolated BCL-2 inhibition between these 2 lymphoid malignancies is that BCL-XL plays a more important role in early lymphoid development as compared with mature B lymphocytes. ALL is a disease of early B lymphocytes, whereas CLL originates from mature B lymphocytes. When comparing BCL-2 family messenger RNA expression for responders vs nonresponders in pediatric ALL xenografts, the only gene found to be significantly upregulated in nonresponders was BCL2L1 (encoding for BCL-XL/Xs). In keeping with this finding, simultaneous targeting of BCL-2 and BCL-XL with venetoclax and A-1135463 induced synergistic killing across multiple ALL xenografts. The one exception identified, where targeting BCL-2 alone appeared to be sufficient, was MLLr-ALL. Previous studies have demonstrated high expression of BCL-2 in MLLr pediatric ALL and shown activity of the 1st generation BCL-2 antagonists in MLLr-ALL, supporting the findings by Khaw et al. It has been recently shown that MLL/AF4 specifically upregulates the BCL-2 gene but not other BCL-2 family members via DOT1L-mediated H3K79 methylation at the BCL-2 locus, and this may explain the higher sensitivity of MLLr-ALL xenografts to venetoclax. These data suggest that venetoclax alone may be the agent of choice in children with MLLr-ALL, whereas navitoclax may be more efficacious in non-MLL pediatric ALL (see figure). However, BCL-XL inhibition is associated with potentially severe on-target thrombocytopenia, limiting the clinical use of navitoclax in acute leukemias. To this end, alternative strategies could be exploited, such as the combined use of selective BCL-2 inhibitors with standard chemotherapeutic agents or mAbs, shown to be highly efficacious in preclinical studies. Notably, several commonly used chemotherapeutic agents were shown to affect the expression of MCL-1 (L-asparaginase and antimetotics) and of BCL-XL (L-asparaginase, dexamethasone, and vincristine). It is anticipated that combinations of venetoclax with established antileukemic agents has the potential to significantly improve the response rates, durability of response, and potentially overcome traditional high-risk features in pediatric ALL.

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