Drug Resistance

Major finding: Increased p110α expression in mantle cell lymphoma sustains constitutive PI3K signaling.

Clinical relevance: A high *PIK3CA/PIK3CD* expression ratio can predict resistance to p110δ inhibition.

Impact: Inhibitors that target both p110α and p110δ may be more effective in mantle cell lymphoma.

p110α CONTRIBUTES TO p110δ INHIBITOR RESISTANCE

The p110δ isoform of the phosphoinositide-3 kinase (PI3K) catalytic subunit is a critical mediator of B-cell receptor (BCR) signaling that is an attractive therapeutic target in B-cell malignancies. p110δ-selective inhibitors have led to durable clinical responses in chronic lymphocytic leukemia and indolent non-Hodgkin lymphomas but have not been as effective in mantle cell lymphoma, an aggressive non-Hodgkin lymphoma that is not curable with conventional chemotherapy. Because amplification of *PIK3CA*, the gene encoding p110α, has been observed in some mantle cell lymphomas, Iyengar and colleagues evaluated whether altered expression or activity of other p110 isoforms could underlie the limited responses to p110δ inhibitor therapy. Of p110α, p110β, and p110δ, only expression of p110α varied among mantle cell lymphoma samples and was significantly upregulated in biopsies taken after relapse. In mantle cell lymphoma cells with elevated p110α expression, a p110δ-selective inhibitor could inhibit BCR-mediated PI3K signaling but did not affect constitutive PI3K signaling. However, a pan-PI3K inhibitor with activity against both p110α and p110δ abolished PI3K signaling and led to significantly greater cytotoxicity in primary mantle cell lymphoma samples than either a p110α- or p110δ-selective inhibitor. Consistent with these findings, a high *PIK3CA/PIK3CD* expression ratio was predictive of p110δ-selective inhibitor resistance and greater response to pan-PI3K inhibition in primary mantle cell lymphoma samples. Interestingly, the *PIK3CA/PIK3CD* expression ratio was also significantly higher in mantle cell lymphomas compared with chronic lymphocytic leukemia and indolent non-Hodgkin lymphomas, providing a potential explanation for the decreased efficacy of p110δ-selective inhibitors in mantle cell lymphomas compared with other B-cell cancers. Together, these findings suggest that high p110α expression may identify patients less likely to respond to p110δ inhibitors and provide support for the clinical development of dual p110α/δ inhibitors in mantle cell lymphoma. ■

Iyengar S, Clear A, Bödör C, Maharaj L, Lee A, Calaminici M, et al. P110α mediated constitutive PI3K signaling limits the efficacy of p110δ-selective inhibition in mantle cell lymphoma, particularly with multiple relapse. Blood 2013 Jan 22 [Epub ahead of print].

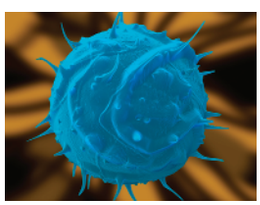
Leukemia

Major finding: The pan–BCL-2 inhibitor sabutoclax sensitizes dormant CML stem cells to dasatinib treatment.

Concept: The bone marrow niche promotes prosurvival BCL-2 family isoform expression and TKI resistance.

Impact: Simultaneous inhibition of multiple antiapoptotic BCL-2 proteins may eliminate cells that drive relapse.

PAN–BCL-2 INHIBITION SENSITIZES LEUKEMIC STEM CELLS TO KINASE INHIBITORS



Tyrosine kinase inhibitors (TKI) that target BCR–ABL eliminate the bulk of chronic myeloid leukemia (CML) cells but do not effectively eradicate quiescent leukemic stem cells (LSC) that can drive relapse and progression from chronic phase to blast crisis. Increased antiapoptotic BCL-2 family protein expression has been associated with leukemogenesis, TKI resistance, and stem cell survival, but because most studies have focused only on BCR–ABL-expressing cell lines the role of BCL-2 family members in LSC maintenance and TKI resistance *in vivo* remains unclear. Goff and colleagues analyzed BCL-2 family member expression in purified progenitor cells from primary normal, CML chronic phase, and CML blast crisis human samples and found that prosurvival BCL-2 family gene isoforms were globally upregulated in blast crisis LSCs. These LSCs caused blast crisis CML upon implantation into recipient mice and robustly engrafted into stem cell niches. Interestingly, quiescent LSCs were enriched in the bone marrow compared with other niches, and even though dasatinib treatment greatly reduced the leukemic burden and inhibited BCR–ABL activity in LSCs, a drug-resistant LSC population persisted in the bone marrow. Compared with LSCs from other tissues, bone marrow LSCs expressed markedly higher levels of *BCL-2* and the prosurvival isoforms of *MCL-1* and *BFL-1*, providing a rationale for testing the effect of sabutoclax, a small molecule that inhibits all prosurvival BCL-2 family proteins, on bone marrow LSC growth. In a stromal coculture system, sabutoclax significantly reduced LSC survival and self-renewal, whereas ABT-737, which only inhibits BCL-2 and BCL-XL, was not as effective. Furthermore, sabutoclax pretreatment sensitized LSCs to dasatinib, and combined treatment of marrow with sabutoclax and dasatinib significantly inhibited primary and serial LSC engraftment and prolonged survival. Pan–BCL-2 inhibition may therefore be useful in combination with TKI therapy to eradicate LSCs in protective niches that drive relapse and disease progression. ■

Goff DJ, Recart AC, Sadarangani A, Chun HJ, Barrett CL, Krajewska M, et al. A pan-BCL2 inhibitor renders bone-marrow-resident human leukemia cells sensitive to tyrosine kinase inhibition. Cell Stem Cell 2013 Jan 17 [Epub ahead of print].