Inhibitors of PI3K/mTOR and histone deacetylases (HDAC) are effective in non-Hodgkin lymphoma (NHL). However, clinical resistance eventually ensues and combinatory therapies are sought to prevent it. Preclinical evaluation of dual PI3K/mTOR and HDAC inhibition is synergistic against NHL, paving the way for bench-to-bedside translation. *Clin Cancer Res;* 20(23); 5863–5. ©2014 AACR.

In a previous issue of *Clinical Cancer Research*, Rahmani and colleagues (1) reported on the synergistic activity of BEZ235 and panobinostat against a panel of non-Hodgkin lymphoma (NHL) cell lines, including the aggressive double-hit lymphoma and activated B cell-like (ABC) subtype of diffuse large B cell lymphoma (DLBCL). NHL is the most common hematologic malignancy in the United States, representing 4% of all cancer, and DLBCL represents the most common subtype, accounting for 25% to 35% of all NHL. DLBCL is a heterogeneous entity classified by the World Health Organization (WHO) as an aggressive B cell lymphoma (2). Although circa 60% of patients with DLBCL can be cured even in advanced stages, prognosis is variable and affected by both host and tumor-related factors. Three distinct molecular profiles with different prognoses have been identified in DLBCL: a germinal center B cell-like (GCB), ABC, and type 3. Patients with ABC subtype DLBCL had a 5-year overall survival rate of 35%, compared with 60% for patients with GCB subtype (*P* value < 0.001) when treated with standard anthracycline-based regimens (3). Even more dismal is the prognosis of patients with double-hit lymphoma, a recently recognized entity currently classified by WHO as a B cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma (2). Double-hit lymphoma is diagnosed based on the concomitant presence of a *v-myc* avian myelocytomatosis viral oncogene homolog (MYC) and a B-cell lymphoma 2 (BCL2), or less often BCL6, gene rearrangement (4).

Median overall survival for these patients is less than 12 months even with high-dose chemotherapy and hematopoietic stem cell transplant. Therefore, the best treatment strategy for these patients remains unclear.

Molecularly targeted therapies have modified the natural history of most cancer, both solid and hematologic, indicating that a better understanding of the molecular mechanisms at the base of oncogenesis and tumor progression is crucial to design novel therapies and eventually cure more patients. It has become increasingly evident that cancer progresses in analogy to the Darwinian theory of the evolution of the species: with time, the founder clone acquires random somatic genetic mutations, originating a number of subclones competing against each other for survival in an environment (the human body and more specifically cancer microenvironment) with limited resources (5). Under the pressure of exogenous stimuli, in particular chemotherapy, subclones are selected according to their capability to survive stress, giving raise to a branching pattern of cancer evolution (6). Unless a single, driver mutation to which cancer cells are addicted (i.e., BCR/ABL rearrangement for chronic myeloid leukemia) is identified, a molecularly targeted monotherapy is unlikely to produce a durable clinical response. Therefore, concomitantly targeting multiple signaling pathways that are predicted to be important for cancer cell survival is a logical approach to circumvent this problem. The major limitation of this approach is the fact that cancer cells typically rely on signaling pathways that are relevant also under physiologic conditions, thus making the therapeutic index of anticancer therapy rather narrow. Epigenetic control of gene expression via histone acetylation and deacetylation and signaling through the PI3K/mTOR/AKT pathway are two examples of molecularly mechanisms hijacked in cancer whose integrity is fundamental for the well-being of healthy tissues. The combination of BEZ235 and panobinostat presented in the article by Rahmani and colleagues (1) appears to be the best of the two world: it successfully inhibits both the PI3K/mTOR/AKT pathway and histone deacetylation and it appears to cause very little toxicity to normal CD34+ bone marrow cells and mice (Fig. 1).
BEZ235 is a dual, pan-PI3K inhibitor and mTOR complex 1/2 (mTORC1/2) inhibitor with retained activity against cells harboring PI3K-activating mutations. BEZ235 was shown to overcome bortezomib resistance in mantle cell lymphoma in vitro (7). PI3K is a family of enzymes divided in three classes, which catalyze the conversion of phosphatidylinositol-4,5-biphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3). PIP3 functions as a second messenger amplifying PI3K signaling by recruiting v-akt murine thymoma viral oncogene homolog 1 (AKT). AKT is activated via phosphorylation by mTORC1 and signals through a variety of effectors, including mTORC2 and Forkhead/winged helix box lass O (FOXO), influencing the function of proteins involved in cell proliferation, differentiation, and apoptosis (8). PTEN dephosphorylates PIP3, thus counteracting PI3K signaling and functioning as an oncosuppressor. PI3K is typically constitutively activated in lymphoma via gene amplification, resulting in increased activity of AKT and mTORC2, thus representing an attractive target for antilymphoma therapy (7). Clinical development of PI3K inhibitors for NHL culminated with the FDA approval of idelalisib in relapsed chronic lymphocytic leukemia/small cell lymphoma and follicular lymphoma (9).

In the study by Rahmani and colleagues, the authors proved that combination of BEZ235 and panobinostat in nanomolar concentrations is cytotoxic against a large panel of NHL cell lines, including double-hit lymphoma, ABC and GCB subtype DLBCL, and mantle cell lymphoma. They showed that when combined, both drugs largely retained their mechanisms of effectiveness, which were typically potentiated by the combination. When combined, BEZ235 and panobinostat did not affect viability and clonogenic potential of progenitor, CD34+ bone marrow cells in vitro and appeared well tolerated by mice in in vivo studies. These considerations suggest that this drug combination could be more effective than core histones and other nonhistone target proteins, causing epigenetic modulation of gene expression and influencing a variety of cellular processes such as cell proliferation, neoangiogenesis, migration, and apoptosis. HDACs are frequently overexpressed in cancer, and broad or selective inhibitors of HDACs have been developed (10).

Vorinostat, a class I and IIb HDAC inhibitor, is currently FDA approved as third-line treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients with progressive, persistent, or recurrent disease (11). Panobinostat is an HDAC class I inhibitor, currently being evaluated in clinical trials in numerous hematologic and solid malignancies, including Hodgkin’s and NHL, multiple myeloma, acute myeloid leukemia, breast adenocarcinoma, and prostate adenocarcinoma (12).
each single agent in the treatment of patients with NHL and that adverse events, in particular myelosuppression, are anticipated to be manageable.

The effectiveness of molecularly targeted therapies is generally limited by attendant toxicities and/or development of resistance related to a variety of molecular mechanisms. This is particularly true for biologically aggressive neoplasia, where multiple, distinct signaling pathways are concomitantly deranged. The close interplay between bench research and bedside clinical activity has played a critical role in identifying such mechanisms and helping design ad hoc combinatorial therapies such as the one presented in the study by Rahmani and colleagues.

References

Team Work Matters: Dual Inhibition Puts Non-Hodgkin Lymphoma Under Siege

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