may differ. In the case of SVT, the traditional paradigm of it being a benign, self-limiting disease treated with anti-inflammatories and warmth is quickly giving way to the recognition of significant morbidity and even mortality. Recent trials of anticoagulants to treat SVT demonstrate reduced progression to VTE and improved patient comfort, both demonstrating reduced progression to VTE.2 trials of anticoagulants to treat SVT similarly to VTE.2

In the case of SVT, many questions remain unanswered. Despite the recommendation that most SVT be treated with anticoagulants, how commonly is this done in clinical practice? Does anticoagulation change the frequency of VTE or mortality following an episode of SVT? What is the role of the newer oral anticoagulants in treating SVT? How often does bleeding complicate treatment of SVT? Harnessing the power of the EHR could help us efficiently gain insight into the answers to these questions. But first, we need to ensure the EHR accurately captures important outcomes in a manner that improves clinical care and can be used for research. Overall, this study conclusively demonstrates that SVT is not a benign disease and has consequences for patients. This study also demonstrates the power of population registries in improving health care. With the advent of EHRs in the United States and other nations, we must focus on how we can accurately record the health and illness of populations with the goal of providing cost-conscious, evidence-based care for everyone.

**Conflict-of-interest disclosure:** The author declares no competing financial interests.

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**LYMPHOID NEOPLASIA**

Comment on Jing et al, page 273

**Yin and yang of glucocorticoid receptors in apoptosis**

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In this issue of *Blood*, Jing et al have identified 2 novel pathways involved in the dexamethasone response in pediatric B-precursor acute lymphoblastic leukemia (ALL).1

Using patient-derived xenografts, the authors show that the glucocorticoid receptor (GR) coordinately regulates both the antiapoptotic protein Bcl2 and the proapoptotic protein BIM (see figure). Using gene expression profiling, chromatin immunoprecipitation (ChIP), and ChIP sequencing (ChIP-seq) analysis, the authors identified a novel intronic GR binding site within the BIM coding region. The group also showed that both the GR promoter in KLF13 and the intronic BIM GR promoter were absent in leukemia cells resistant to dexamethasone.
As with most accounts of apoptosis regulation, GR regulation of apoptosis in leukemia cells is both elegant and complex. In dexamethasone-sensitive patient-derived xenografts, Bcl2 is indirectly mediated through KLF13 and MYB (panel A), resulting in decreased production of Bcl2. In addition, GR increases the expression of BIM, resulting in Bcl2 inhibition. In dexamethasone-resistant leukemia cells, the GR does not hinder Bcl2 binding to BAX, resulting in an inhibition of apoptosis (panel B). Thus, the authors identified novel mechanisms for the GR to both decrease Bcl2 production and inhibit Bcl2 function.

The results of this article are compelling for 2 reasons. First, the authors use a clinically relevant model of pediatric ALL xenografts. The leukemia cells used for this analysis are cells derived from pediatric patients with ALL that have been expanded and maintained in immunodeficient NOD/SCID mice. These cells are more likely to have maintained the growth characteristics and signal transduction pathways of leukemia patients than established cell lines are.

Second, the results have clinical implications. Sensitivity to glucocorticoids is one of the main predictors of ALL chemosensitivity and is an indicator of drug responsiveness in many pediatric clinical trials. Approximately 10% of patients with ALL have a poor response to steroid treatment, a characteristic associated with significantly inferior outcome. Glucocorticoid resistance in leukemia cell lines is often due to the absence of the GR; however, many patient-derived leukemia cells with glucocorticoid resistance have functional GRs. The mechanisms of glucocorticoid resistance in patient-derived samples has been previously linked to Bcl2, BIM, and Mcl1. This article provides further insight into how Bcl2 regulates glucocorticoid resistance and suggests that GR resistance could be mediated through absent intronic GR promoters in BIM or the absence of GR promoters for KLF13.

Strategies that reverse glucocorticoid resistance could have a significant impact in increasing overall clinical survival, particularly for high-risk leukemia groups such as infants with the MLL translocation and patients with NOTCH-mutated T-cell ALL. Agents known to increase glucocorticoid sensitivity, such as proteasome inhibitors, are currently undergoing clinical trials for pediatric ALL in the United States (NCT02112916). This research work is particularly interesting when considered with studies showing that proteasome inhibition can increase BIM expression in chronic lymphocytic leukemia (CLL) by inhibiting BIM degradation, leading to enhanced CLL apoptosis in patient CLL cells that are treated with both dexamethasone and the proteasome inhibitor MG132.

Several strategies have been explored to enhance the glucocorticoid-mediated apoptosis of leukemia cells in preclinical studies, including use of mTOR inhibitors, glycolysis inhibitors, and γ-secretase inhibitors. Despite a slow start due to liver toxicity in earlier clinical trials, several γ-secretase inhibitors are currently in early-stage clinical trials for solid tumors and T-cell ALL. Restoring glucocorticoid sensitivity could not only improve clinical outcome in high-risk groups with newly diagnosed ALL but also improve response rates in patients with difficult-to-treat relapsed ALL. As novel treatment strategies are developed to improve ALL survival, it may be helpful to revisit and perhaps reinvigorate chemotherapy agents that have a proven track record in ALL. Thus, novel treatment strategies may improve ALL survival by reinvigorating one of the most commonly used and effective chemotherapy agents in ALL.

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REFERENCES
Novel target to kill CLL

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In this issue of Blood, Liu et al report on OSU-T315, a new agent that specifically disrupts the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway and shows high proapoptotic activity against chronic lymphocytic leukemia (CLL) cells, which may indicate a potential therapeutic application in this disease.1

Great progress has been made in the diagnosis and treatment of CLL, but this type of leukemia still remains incurable, and the introduction of new drugs and new therapeutic strategies are still awaited. For the last 20 years, significant progress in molecular biology has resulted in better characterization and understanding of the biology and prognosis of CLL. Accumulating evidence supports the critical role played by B-cell receptor (BCR) activation in the pathogenesis of CLL and has provided new opportunities for the development of innovative, more effective therapies. Recently, several small molecular kinase inhibitors targeting the proximal BCR signaling pathway, including Bruton’s tyrosine kinase (BTK) inhibitor, ibrutinib, and phosphatidylinositol 3-kinase p110δ (PI3Kp110δ) inhibitor, idelalisib, have been developed (see figure). These drugs are part of a promising new strategy for the effective targeted treatment of CLL and have been recently approved by the US Food and Drug Administration.2,3

Among the new therapies intended for CLL, much attention is being paid to the implementation of agents with a high potential for triggering apoptosis of tumor cells.4 The PI3K/AKT signaling pathway plays a pivotal role in regulating multiple cellular events supporting the survival of CLL B cells. In CLL, activation of the PI3K/AKT pathway has an important role in the generation of the proliferative pool, and the pharmacological compounds that disrupt this pathway may have significant antiproliferative activity.5 Studies based on the coculture of CLL cells with marrow stromal cells show that PI3K/AKT signaling plays an important role in the activation of both cell types during their interactions that support survival of CLL tumor cells.6 OSU-T315 is an inhibitor of the PI3K/AKT pathway, which exhibits high in vitro potency against a panel of prostate and breast cancer cell lines.7 Liu et al report their results of a study comparing the activity of OSU-T315 in both CLL-derived cell lines and primary CLL cells with its action in normal lymphocytes. They document a unique mechanism of OSU-T315 action. Namely, the compound directly abrogates AKT signaling by preventing the translocation of AKT kinase into lipid rafts. Importantly, in this mechanism, the activation of receptor-associated kinases remains unaltered. As a consequence, OSU-T315 induces caspase-dependent apoptosis by suppressing BCR, CD49d, CD40, and Toll-like receptor 6-mediated AKT activation in CLL cells. This mechanism is independent of the integrin-link kinase.3 Moreover, in a transplant TCL1 mouse model, OSU-T315 prolongs the survival of leukemic mice by the selective targeting of CLL cells and sparing of normal B or T lymphocytes. In addition to OSU-T315, other AKT inhibitors exert antileukemic activity. The best sample is MK2206, a highly selective oral allosteric AKT inhibitor found to exert the in vitro efficacy of MK2206 on CLL B-cell survival.8 MK2206 abolishes phosphorylation of AKT3473, significantly
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