Targeting kinases in CML and CLL

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Whereas kinases have become effective targets for cancer treatment, such enzymes have not been recognized as therapeutic targets in CLL. In this issue of Blood, Herman et al demonstrate expression of PI3K-δ in CLL and introduce CAL-101, a selective inhibitor of this kinase.1

Among the hematologic malignancies, the genetic lesion in chronic myelogenous leukemia (CML) resulting in Bcr-Abl tyrosine kinase has become a hallmark target for therapeutic intervention. Inhibition of Bcr-Abl tyrosine kinase is a poster child for kinase-targeted therapeutics. Unlike CML, chronic lymphocytic leukemia (CLL) does not have a genetic lesion associated with the pathophysiology or biology of the disease. However, in recent years, a few kinases have been identified that compared with normal lymphocytes are overexpressed, constitutively active, or activated by microenvironment factors in pathogenic CLL cells. Corollary to this, selective small-molecule inhibitors of these kinases provide a new pharmacopeia for CLL (see figure) where for decades nucleoside analogs, alkylating agents, and immunotherapeutics have remained the mainstay in treating this disease.

Mature B lymphocytes are essential antibody-producing cells of the immune system with B-cell receptors (BCRs) that recognize foreign antigens. Signals emanating from the BCRs are responsible for development/mutation, proliferation, maintenance, and activation of normal B lymphocytes.2 Several kinases cooperate with BCR and amplify its signaling cascades. These signaling events are not only prevalent but are overexpressed in malignant B lymphocytes like B-cell CLL.3 In addition, microenvironment interactions further augment similar and same survival pathways in CLL cells. These molecular and cellular biology revelations have identified several kinases that play a strategic and important role in CLL pathophysiology. After understanding the impact of these enzymes, inhibitors have been designed, developed, and tested and have opened up a new horizon in CLL therapy.4

A key mediator of proximal BCR signaling is spleen tyrosine kinase (SYK), which is activated through sequential phosphorylation. The downstream pathway is quite involved and eventually leads to activation of Erk and transcription factors.5 In CLL, this protein kinase is overexpressed and downstream signaling of this enzyme contributes to CLL cell survival.6 A selective inhibitor of this kinase, R406, showed activity in primary CLL lymphocytes that were cocultured with bone marrow stroma cells.7

One of the downstream kinases that is activated by SYK is Bruton tyrosine kinase (BTK), which is an intermediary enzyme in the BCR signaling pathway. It is a cytoplasmic enzyme that is essential in B lymphocyte development, survival, and signaling.8 PCI-32765 is a small-molecule BTK inhibitor that forms a specific and irreversible bond with cysteine 481 of the enzyme.

In addition to BCR signaling, several lines of evidence suggest a role for B lymphocyte stimulator (BLyS), a tumor necrosis factor superfamily ligand, in B-cell survival and resistance. BLyS stimulation activates 2 independent signaling pathways, Akt/mTOR and Pim-2.9 The downstream and target molecule of the BLyS-dependent signaling is the antiapoptotic protein Mcl-1, which has been a hallmark factor for CLL cell survival.10 Pim kinase overexpression was demonstrated in CLL cells and a selective Pim kinase inhibitor, SGI-1776, showed cytotoxicity in pathogenic CLL cells without an effect on normal B lymphocytes.11

In the current article, the authors show the importance of yet another kinase, PI3K, in CLL cell survival. The isoform delta of the
enzyme is overexpressed in CLL B lymphocytes compared with normal B lymphocytes and, more importantly, the activity of this enzyme is higher in leukemic lymphocytes. Although not done, because the recombinant protein is available, a serial dilution of this protein will allow for quantitation of the exact amount of PI3Kδ isoform in normal and malignant lymphocytes. The group introduces us to a selective inhibitor of this isoform, CAL-101. It is not clear whether the expression level of this protein is correlated with the biological effect of CAL-101, as T lymphocytes that express high levels of this protein were not affected by this agent. Compared with the direct biological effect of CAL-101 on CLL lymphocytes (which was marginal), the impact on cytokine production of T and NK cells was impressive and was consistent with the role of PI3Kδ in T-cell cytokine production. The mechanism for this effect, however, was not explored and remains elusive.

The authors identify mechanisms of CAL-101–induced CLL cell death; they show a decrease in Akt phosphorylation, which occurs through the PI3K pathway. In addition, it inhibited phosphorylation of GSK3β. These signaling pathways are associated with Mcl-1 stability and may have been responsible for a decrease in Mcl-1 protein levels in CLL cells and cell death after CAL-101 treatment. Furthermore, CAL-101 disrupted interactions of CLL cells with microenvironment stimuli. The obvious question, which arises from these preclinical investigations with a variety of kinase inhibitors, is their efficacy in the clinic. Although these are early investigations, recent clinical trials suggest that these agents have potential. With the first clinically used BTK inhibitor, fostamatinib (which is a prodrug of R406), a response rate of 55% was achieved in previously treated small lymphocytic leukemia (SLL)/CLL (n = 11). Similarly, recent clinical results with PCI-32765, a small-molecule BTK inhibitor, resulted in complete response and partial responses in 13 CLL/SLL patients with a pharmacodynamic end point suggesting occupancy on BTK by the drug. Pim kinase inhibitor has not been evaluated in patients with CLL, but the first clinical investigation is ongoing (http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=637010&version=HealthProfessional&protocolsearchid=7912622). Finally, phase 1 studies in relapsed/refractory hematologic malignancies with oral CAL-101 resulted in a 30% overall response rate in CLL (n = 33). The pharmacokinetic and pharmacodynamic investigations demonstrated biologically required concentrations of the drug (1–7 μM) with a decline in phosphoAkt in target pathogenic B lymphocytes.

In conclusion, as opposed to conventional cytotoxic chemotherapy, pathophysiology of CLL lymphocytes and their interactions with the microenvironment milieu offer untested opportunities to tailor therapeutic options for patients with CLL. Understanding of the molecular and cellular biology of CLL, albeit at infancy stage, has provided novel kinase targets (previously allied to CML) to change the therapeutic strategies for this B-cell lymphocytic neoplasm. Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

A decade of R-CHOP

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Initial results of the first randomized trial evaluating the addition of rituximab to CHOP for DLBCL were reported in December 2000, ushering in the new millennium by delivering on the promise of targeted therapy. In this issue of Blood, Coiffier et al—having reached a median follow-up of 10 years—confirm a sustained survival benefit and a cure rate for elderly patients that is over the 50th percentile with the simple addition of a monoclonal antibody targeting CD20 to the “gold standard” chemotherapy. The magnitude of this advance cannot be overstated, as the intergroup trial comparing third-generation regimens to CHOP demonstrated that the limits of chemotherapy alone had apparently been reached.

With R-CHOP (rituximab–cyclophosphamide, doxorubicin, vincristine, and prednisone), the 10-year progression-free and overall survival rates for elderly patients with advanced-stage diffuse large B-cell lymphoma (DLBCL) are 36.5% and 43.5%,
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