Comment on Herman et al, page 2078

Targeting kinases in CML, 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 pharmacopoeia for CLL (see figure) where for decades nucleoside analogs, alkylating agents, and immunotherapeutics have remained the mainstay in treating this disease.

CLL cells do not have any selective genetic lesion that is associated with the pathophysiology of the disease. On the contrary, B-cell receptor–mediated signaling and interactions with the microenvironment have been shown to maintain CLL lymphocytes. Unlike a single kinase, Bcr-Abl in CML, CLL offers several kinases to target, and selective small-molecule kinase inhibitors are recognized and tested. PI3K indicates phosphatidylinositol 3-kinase; SYK, spleen tyrosine kinase; and BTK, Bruton tyrosine kinase. Professional illustration by Marie Dauenheimer.

A new pharmacopoeia for CLL (see figure) where for decades nucleoside analogs, alkylating agents, and immunotherapeutics have remained the mainstay in treating this disease.

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

Abbreviations used:
- BCR: B-cell receptor
- Bcr-Abl: B-220: B-cell antigen
- BLyS: B lymphocyte stimulator
- BTK: Bruton tyrosine kinase
- Mcl-1: Myeloid cell leukemia sequence 1
- PI3K: Phosphatidylinositol 3-kinase
- SYK: Spleen tyrosine kinase
- Bcr-Abl: Breakpoint cluster region–Abelson murine leukemia viral oncogene homolog

References:
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 (1–7μM) 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 untasted 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.

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REFERENCES

Comment on Coiffier et al, page 2040

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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