Comment on Friedberg et al, page 2578

Syk [sic] of the same old chemotherapy?

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In this issue of Blood, Friedberg and coworkers present the first report of fostamatinib disodium, a Syk inhibitor, as an active treatment for patients with B-cell non-Hodgkin lymphomas and chronic lymphocytic leukemia.1

After decades of chemotherapeutic ennui, comparing various drug acronyms, treatment for patients with B-cell malignancies became relatively exciting with the availability of active and well-tolerated monoclonal antibodies, notably the anti-CD20 rituximab. Finally, survival was prolonged in patients with diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Nevertheless, 30% to 40% of patients with DLBCL still die from their disease, and the indolent and mantle cell lymphomas and CLL remain incurable. Moreover, the nonspecific chemotherapies with which the antibody was combined induce significant toxicities.

A greater understanding of the biology and genetics of these tumors has resulted in an almost exponential increase in the number of targeted therapies. These range from numerous monoclonal antibodies, to others capable of activating or inhibiting intracellular pathways, including AKT-mTOR, PI3-kinase, the intrinsic and extrinsic apoptotic pathways, and numerous others. Even beyond targeting the malignant cell has been the recent recognition of the importance of the tumor microenvironment.

The current study focuses on a drug that targets a pathway activated by the B-cell receptor (BCR). BCR signaling is important during B-cell ontogenesis and is key to the survival of malignant B cells. The survival of most B-cell lymphomas, most notably DLBCL, may depend on the non–ligand-dependent ("tonic") signals from the BCR. These effects are amplified by spleen tyrosine kinase (Syk), a cytoplasmic tyrosine kinase that is important in mediating immunoreceptor signaling in B cells, as well as macrophages, neutrophils, and mast cells. The downstream events are regulated by a balance between the protein tyrosine kinase Syk activation and protein tyrosine phosphatase–mediated inhibition of Syk. In vitro inhibition of Syk induces apoptosis of a number of lymphoma cell lines. Considering the importance of BCR in B-cell survival in normal B cells and lymphoma cells, Syk appears to be a reasonable therapeutic target.2

Fostamatinib disodium is an oral prodrug that is rapidly converted to R406, a potent inhibitor of Syk. In rheumatoid arthritis, Syk expression has been detected in the synovial tissue. Syk also associates with the FcgammaR in macrophages and other inflammatory cells, thought to be responsible for clearance of platelets in idiopathic thrombocytopenic purpura. In both of these disorders, fostamatinib has demonstrated clinical efficacy with excellent tolerability.

In the current phase 1/2 study,1 fostamatinib was well tolerated; the most serious adverse effects included myelosuppression, fatigue, and diarrhea, which were rarely severe. The study patients had received a median of 4 previous therapies. Nonetheless, responses...
occurred in one-quarter of patients, with responses being more common in patients with CLL/SLL (54.3%) and DLBCL (23.5%), and less common in follicular lymphoma (9.5%) or mantle cell lymphoma (11.1%). Evidence of clinical activity was also noted in a number of other patients, although it was insufficient to qualify for a response. The median progression-free survival was 4.1 months for all patients.

Other than CLL/SLL, the response rates with fostamatinib were modest. However, single-agent activity is not essential for pursuing a novel targeted agent. The role of such drugs may primarily be to enhance the efficacy of other agents. Perhaps the poster child for this effect is bevacizumab (Avastin; Genentech Biooncology). Recent data suggest that, at least in CLL, the combination of R-406 with fludarabine increases cytotoxicity compared with fludarabine alone. Moreover, in B-CLL cells, the cytotoxic effects of Syk correlates with Syk expression. B-cell diseases are markedly heterogeneous, even within histologic subtypes, as has been repeatedly demonstrated by gene-expression profiling and other technologies. Thus, differences in response may reflect variability in the inherent biology of a specific tumor. The goal is to individualize lymphoma therapeutic strategies based on molecular/genetic features of the tumor and pharmacogenomic characteristics of the patient. Therefore, it is critical to include correlative studies within clinical trials to demonstrate whether the relevant target is actually affected. Future strategies based less on nonspecific cytotoxics and more on combinations of targeted therapies directed at different receptors and pathways will bring us closer to limiting untoward effects while enhancing efficacy, resulting in cure of patients with B-cell malignancies.

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REFERENCES

There’s many a CLP on the path to B

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Lymphocyte development is an excellent model system to study cell fate choices and the underlying transcriptional mechanisms. However, the earliest events have been poorly understood, due in part to the rarity of the relevant cellular intermediates. In this issue of Blood, Mansson and colleagues identify several subsets within the CLP and fraction A population (B220<sup>+</sup> CLP phenotype) with differing lineage potentials. The results indicate that B-lineage restriction initiates at much earlier developmental stages than previously thought and provide insight into the hierarchical transcriptional mechanisms involved in B-lineage commitment.

How common lymphoid progenitors (CLPs) give rise to B lineage–restricted progeny is unclear. The B lineage–specific transcription factor Pax5 is critical for B-cell development, and it was suggested that expression of Pax5 as visualized by up-regulation of its gene target CD19 on progenitors drove B-cell lineage commitment. However, CD19<sup>-</sup> CLPs express transcriptional regulators important for B-cell lineage commitment including Ebf1 and Pax5, but surprisingly still maintain non–B-cell lineage potentials. Mansson et al used mice transgenic for reporter of RAG1 and Igll1 (itself a transcriptional target of Pax5) to identify substantial heterogeneity within the CD19<sup>-</sup> CLP/fraction A pool. The authors identified in this early progenitor compartment some cells that were RAG1<sup>iso</sup>, other cells that were RAG1<sup>hi</sup> but negative for Igll1 (referred to here as RAG1<sup>hi</sup>), and finally cells that were RAG1<sup>hi</sup> and also positive for Igll1 (referred to here as Igll1<sup>+</sup>). In vitro cell culture established that these newly identified populations were linearly related, with a developmental sequence of RAG1<sup>iso</sup> to RAG1<sup>hi</sup> to Igll1<sup>+</sup>.

Consistent with this proposed relationship, the earliest RAG1<sup>iso</sup> cells had the broadest set of lineage potentials, maintaining natural killer (NK), B, T, and even a degree of myeloid potential in clonal assays. The potential to generate NK cells and also myeloid cells appeared greatly decreased by the RAG1<sup>hi</sup> stage (see figure). This finding is supported by other recent data showing that RAG1 expression in CLP marks diminished NK-cell potential at the population level. Expression of the cell-surface marker Ly6D correlated with increased expression of the RAG1 reporter and also coincided with loss of NK-cell potential. Other recent work has found that the Ly6D<sup>+</sup>...
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