How has the understanding of the pathophysiology of chronic lymphocytic leukemia (CLL) advanced in recent years?

There has been a dramatic increase in the understanding of CLL on a number of different fronts. One of the areas that I have been particularly interested in and have worked in concerns the definition of some of the genetic mutations that are involved in CLL. We have identified pathways that were not previously known or expected to be involved in CLL, such as the NOTCH signaling pathway, as well as splicing factors like SF3B1. This has opened up a whole new realm of potential pathophysiology in CLL that was not anticipated.

Another area of focus is genetic susceptibility, where genomewide association studies have identified alleles that are potentially involved in causing CLL. We do not know what the targets of those alleles are just yet. There is interest in applying genome sequencing techniques to try and better understand some of those alleles, as well as the underlying genetic susceptibility to CLL more broadly.

Another big area has been in the characterization of the B-cell receptors (BCRs). Approximately 30% of CLL cases have what are called stereotyped BCRs, where CLLs from entirely different individuals actually have the same or very similar BCRs, which is statistically a vanishingly unlikely event. This suggests that there may be a component of the disease that is antigen-driven.

The importance of the microenvironment in CLL has become even more prominent in recent research. CLL cells circulate in the peripheral blood and then become attracted into the lymph nodes and bone marrow, where there is much more of a microenvironment that provides support to the cells. The lymph node and bone marrow niches are likely the sites where most CLL cells grow, divide, proliferate, and expand. Preventing such growth and development on those sites fuels a lot of novel research.

What is known about the BCR pathway and its role in CLL?

The BCR pathway includes the immunoglobulin gene in the membrane. Binding of antigen to the immunoglobulin triggers phosphorylation of ITAM tyrosine residues by the kinases Lyn and Syk. This then triggers a second messenger cascade through activation of Syk, Lyn, and Bruton’s tyrosine kinase (BTK), with subsequent propagation through phosphatidylinositol 3-kinase (PI3K)/Akt, MAPK, and NF-κB pathways. This ultimately leads to B-cell activation and proliferation. The degree of activation of the pathway at baseline, and the effects of activation of the pathway, vary in different CLL prognostic categories, for example based on the mutational status of the variable immunoglobulin genes (IGHV) and ZAP70 expression.

What are the concerns of current treatment approaches?

The most active therapeutic regimens used today are combinations of conventional chemotherapy with rituximab (Rituxan, Genentech/Biogen Idec). Such regimens are highly effective in both initial and relapsed treatment settings, and yield excellent overall response rates. However, they are less effective in certain patient subsets, such as those with loss of normal p53 activ-
ity due to deletion of chromosome 17p, patients with somatic mutation of p53, and patients with unmutated IGHV. Furthermore, these therapies are associated with significant morbidity as a result of myelosuppression and immunosuppression. This often necessitates dose reduction or truncation of treatment, and discourages use in elderly patients who often cannot tolerate these therapies and whose effective treatment options are therefore more limited.

**H&O What are some targeted inhibitors that have shown promise?**

**JB** The 2 main targets that have had highly active inhibitors in the clinic thus far are PI3K and BTK. PI3K is a key downstream mediator of BCR signaling, and it comes in a variety of different isoforms. There are 4 class I isoforms, and alpha and beta isoforms are broadly expressed in all cell types, whereas delta has expression largely limited to hematopoietic cells and, most importantly, in B-cells. There is a lot of interest in focusing on delta inhibition in particular as a target in B-cell malignancies. The drug that first came into the clinic was idelalisib, which has demonstrated high potency with rapid durable lymph node responses. We will be presenting final data from our phase I study of idelalisib at the 2013 American Society of Clinical Oncology annual meeting (Abstract 7003). This study included 54 patients with refractory or relapsed CLL whose disease had worsened despite having received a median of 5 prior therapies. The average duration of idelalisib treatment was 9 months. There was rapid tumor reduction with clinical benefit in approximately two-thirds of patients, which generally occurred in the first 2 months after starting therapy. Irelalisib delayed disease progression by an average of 17 months, which is much better than that typically expected for a six-line therapy. Disease symptoms like fatigue were decreased in many patients. Those who benefited from the drug were able to continue treatment on an extension study. In general, the lymph node responses have been very deep, at over 80%, accompanied by lymphocytosis. This pattern of response is common with inhibitors of any of the kinases that are downstream of the BCR. The increase in lymphocytosis is likely due to redistribution of CLL lymphocytes from the lymph nodes into the peripheral circulation. This temporary rise in circulating CLL lymphocytes complicates treatment response assessment, because classic criteria for complete and partial responses require resolution or reduction in both lymphadenopathy and lymphocytosis. We observed that the total responding patient population was 72%, based on patients who experienced a typical partial response where the white blood cell count and lymph nodes decreased (39%), as well as patients who experienced nodal responses and an improvement in cytopenias, such as platelet count and hemoglobin levels, despite the fact that their white blood cell count remained high (33%).

With regard to BTK inhibition, ibrutinib is the lead drug in this category. As with other inhibitors of the BCR pathway, ibrutinib causes rapid nodal reduction and response associated with rapid increase in lymphocytosis, which returns to baseline over time. Researchers have examined which patients have more rapid resolution of the white count. Interestingly, one study by Byrd and colleagues suggests that it may be correlated with the IGHV mutational status. The IGHV mutational status refers to the BCR gene in CLL, and the degree to which it has been changed from the original gene that patients were born with. That also correlates with the degree of activation of the BCR signaling pathways. Among higher-risk patients (the so-called unmutated IGHV patients), there tends to be more rapid resolution of lymphocytosis. That observation has not been confirmed in other studies or with other inhibitors yet, but it is nonetheless intriguing.

Ibrutinib phase II data look very promising. The results of the aforementioned 116-patient phase Ib/II trial were presented at the 2012 American Society of Hematology (ASH) annual meeting (Abstract 189). Treatment-naive CLL patients who received ibrutinib monotherapy had a 68% overall response rate, which included a complete response rate of 10%. The estimated progression-free survival rate for the 31 patients in this cohort was 96% at 26 months. Relapsed/refractory patients had a 71% overall response rate, and the response rate was not different in higher-risk patients, including those with 17p deletion or bulky lymphadenopathy. The combined progression-free survival at 26 months for the relapsed, refractory, and high-risk patients was 75%. Unlike other CLL agents, ibrutinib was not myelosuppressive. Most of the side effects in this study were grade 1 or 2 and often resolved after the first few cycles of therapy.

**H&O What are the biggest remaining challenges?**

**JB** Patients with 17p deletion are a remaining challenge. Even though they respond to these drugs, it appears that they are still relapsing, and doing so earlier than other patients. Thus, we may need to combine these drugs with each other and with other targeted inhibitors, or with more traditional treatments like chemoimmunotherapy. It has been suggested that there might be a higher rate of transformation or more explosive disease progression in patients who relapse on these drugs. If this proves to be true, critical questions will need to be addressed. What are the mechanisms of resistance? Will such mechanisms allow patients who are progressing on one drug to respond to another drug that inhibits a different place within the
pathway? These investigative studies are largely in their infancy because we are just starting to accumulate reasonable numbers of patients who have been on these drugs, some of whom are starting to relapse.

Even though we are seeing good prolonged partial remissions with these inhibitors, we do not yet know how long such partial remissions will remain stable. If resistant clones eventually grow out, we must then determine whether it would be better to continue trying to get patients into deeper remissions, complete remissions, or even minimal residual disease (MRD)-negative complete remissions at the beginning of therapy. How we will accomplish such goals with these drugs will likely involve combinations, perhaps with chemoimmunotherapy or with other targeted agents.

H&O What does the future hold?

JB Working to combine these agents to achieve deeper and longer remissions in patients is a viable goal. Ultimately, combinations of multiple targeted therapies may be the best approach in terms of both tolerability and efficacy. Hopefully, we will eventually be able to give patients multiple oral drugs, similar to the way in which we treat high blood pressure, to control their CLL. These are some relevant aspirations for the community.

Suggested Readings


Byrd JC, Furman RR, Coutre S, et al. The Bruton’s tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765) promotes high response rate, durable remissions, and is tolerable in treatment naïve (TN) and relapsed or refractory (RR) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) patients including patients with high-risk (HR) disease: new and updated results of 116 patients in a phase Ia/II study. Blood (ASH Annual Meeting Abstracts). 2012;120: Abstract 189.
