Progress in Chronic Lymphocytic Leukemia with Targeted Therapy

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For decades, the treatment of chronic lymphocytic leukemia (CLL) has relied on cytotoxic drugs with incremental benefit from anti-CD20 monoclonal antibodies. However, in the past 5 years, targeted drugs have fundamentally changed the management and outcome of CLL. In this issue of the *Journal*, two studies describe the use of second-generation drugs. In one of the studies, Byrd et al. target Bruton's tyrosine kinase (BTK) with the use of acalabrutinib, and in the other, Roberts et al. target B-cell lymphoma 2 protein (BCL2) with the use of venetoclax. In each case, the second-generation agents appear to improve substantially on the specificity of their first-generation siblings, ibrutinib and navitoclax, respectively.3,4

These advances derive from programs that target proteins in key pathways in B-cell biology and pathogenesis. Among these is BTK, a component of the B-cell receptor (BCR) pathway that was hypothesized to drive CLL proliferation and survival.5 The development of ibrutinib, an irreversible inhibitor of BTK, challenged the notion that covalent inhibition would cause unacceptable toxicity owing to excessive kinase suppression. However, it was the ability of ibrutinib to robustly inhibit BTK that produced effective inhibition of BCR signaling and established the role of BCR signaling in CLL.3 Like many targeted drugs, ibrutinib has off-target effects that may contribute to both its effectiveness and its toxicity (Fig. 1A). In particular, ibrutinib inhibits interleukin-2 inducible T-cell kinase (ITK) and TEC protein tyrosine kinase, key components of T-cell activation and regulators of the immune response and migration of type 2 helper T cells.9 Although it has been proposed that skewing of type 1 helper T cells by ibrutinib reduces infections and inhibits survival niches for CLL, it also diminishes the rituximab-dependent activity of natural killer cells.7 Inhibition of TEC kinase interferes with platelet aggregation and may contribute to bleeding, a clinical side effect of ibrutinib, whereas suppression of signaling by epidermal growth factor receptor (EGFR) may be a major cause of the commonly observed rash.3,8 Although honing the binding specificity of a drug may improve toxicity and efficacy, the contributions of off-target inhibition are unpredictable.

In their report on acalabrutinib, Byrd et al. provide compelling evidence of decreased toxicity. Acalabrutinib, which was developed on the basis of its high degree of BTK inhibition, significantly reduced binding to ITK, TEC, and EGFR (Fig. 1A). Clinically, no bleeding was observed with acalabrutinib, and the incidence of rash may be lower than that observed with ibrutinib.9 In addition, acalabrutinib showed durable activity across molecular prognostic groups, confirming the importance of selective BTK inhibition. The short half-life of acalabrutinib allowed twice-daily administration and near-total BTK inhibition, an effect that may reduce drug resistance. Ultimately, a randomized comparison of acalabrutinib and ibrutinib is needed to assess meaningful differences.

The prosurvival BCL2 proteins also play a central role in lymphocyte biology, where they...
regulate clonal selection and survival and are expressed in CLL.\textsuperscript{10,11} Employing structure-based design to identify small molecules that bind BCL2-like protein 1 (BCL-xL), investigators developed the first-generation high-affinity inhibitor of BCL2 family proteins (Fig. 1B).\textsuperscript{12} This agent, navitoclax, enhanced the effect of death signals and killed cells in a mechanistically canonical manner.\textsuperscript{13} Consistent with its structure-based design, navitoclax also inhibited BCL-xL and BCL2-like protein 2 (BCLW). A phase 1 study of navitoclax showed activity in 50\% of patients with relapsed or refractory CLL, but the drug was associated with dose-limiting thrombocytopenia owing to the inhibition of BCL-xL, a regulator of platelet senescence.\textsuperscript{4} To generate a more potent and selective BCL2 inhibitor, investigators reverse-engineered navitoclax and related structures through the systematic removal or replacement of key binding elements.\textsuperscript{14} This effort led to the development of venetoclax, a potent inhibitor of BCL2 with 100 times less activity against BCL-xL (Fig. 1B). Consistent with its binding characteristics, venetoclax showed markedly less thrombocytopenia but more neutropenia (because of potent BCL2 inhibition) than navitoclax. Furthermore, patients with a relatively high tumor burden risked severe tumor lysis, necessitating a ramped dosing schedule. In the study by Roberts et al., venetoclax showed robust activity, with response rates of 71 to 79\% across molecular prognostic groups and a 15-month rate of progression-free survival of 69\% at the expansion dose.

The transformative characteristics of acalabrutinib and venetoclax arise from effective targeting of important survival pathways in CLL. Indeed, BTK inhibition produces durable responses, improves survival, and selects for mutations in the BTK-binding domain.\textsuperscript{15} Whether better BTK occupancy as seen with acalabrutinib will reduce the emergence of resistance remains to be seen. Unfortunately, BTK inhibition rarely induces complete remission, indicating that BCR signaling is not critical for survival of all CLL cells or, alternatively, that sufficient inhibition is
not achieved.16 BCL2 also plays an important role in CLL survival, as indicated by the activity of venetoclax, but complete remission is also infrequent, which is probably a result of the up-regulation of alternative BCL2 family members.17 In vitro, venetoclax and BTK inhibitors are synergistic, which suggests that this combination may further transform the targeted treatment of CLL.17

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The Clearer BENEFITS of Belatacept

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“in the long run,” the economist John Maynard Keynes wryly observed in his 1923 A Tract on Monetary Reform, “we are all dead.” Given the logistic barriers to performing long-term studies of immunosuppression in kidney-transplant recipients, as well as the associated expense, many transplant professionals are similarly pessimistic about how to determine adequate long-term regimens in the current era, in which short-term results are excellent but late transplant loss remains a vexing problem. More than 14,000 of the 101,000 patients listed for kidney transplantation are awaiting repeat transplantation.1 Mechanisms of late transplant loss remain under investigation; toxic effects of calcineurin inhibitors and chronic damage mediated by antibodies directed at the donor kidney are probably major contributors to such loss.

In this context, the study by Vincenti and colleagues in this issue of the Journal2 provides welcome data about long-term outcomes of kidney-transplant recipients who receive immunosuppression with belatacept, a non-nephrotoxic fusion protein that blocks T-cell costimulation.3 The authors report that, according to 7 years of follow-up data from the Belatacept Evaluation of Nephroprotection and Efficacy as First-Line Immunosuppression Trial (BENEFIT), the original phase 3 clinical trial of belatacept, 40 of 221 patients in the cyclosporine group either died or had graft loss, as compared with 26 of 226 in the less-intensive belatacept group and 25 of 219 in the more-intensive belatacept group. These differences are significant, with a hazard ratio for death or graft loss of 0.57 for both belatacept regimens as compared with cyclosporine, and occurred even though acute rejection was more common with belatacept (24.4% with more-intensive belatacept and 18.3% with less-intensive belatacept) than with cyclosporine (11.4%). A similar difference was not observed in the companion study, BENEFIT–Extended Criteria Donors (BENEFIT-EXT), which involved lower-