mice than in those of wild-type mice, indicating that CXCR4 must affect DC migration in a way unrelated to CCR7. One possibility is that failure to desensitize CXCR4 leads to retention of DCs in the skin, or the lymphatics, because both tissues produce CXCL12.

Another question is why a reduction in skin DC migration would be associated with increased inflammation? One possibility relates to the immunoregulatory activity of LCs. After migrating to cutaneous LNs, LCs induce anergy, deletion of allergen-specific $CD8^+$ T cells, and activation of $Foxp3^+$ T-regulatory cells.[5] Thus, a reduction in LC migration in the *Cxcr4*$^{+/1013}$ mice might inhibit immunotolerance and lead to increased inflammation, whereas reduced migration of dermal DCs might inhibit protective immune responses and lead to increased pathogen load. In this regard, it is noteworthy that mutations of other genes that promote DC migration can also lead to enhanced immune responses and autoimmunity. For example, mice lacking CCR7 display increased responses in models of asthma and develop autoimmunity,[6] and mice with a DC-specific deletion of *Ikkb* display impaired DC mobilization from the skin and develop spontaneous autoimmunity,[7] although in these 2 mouse strains, the impaired migration likely results from the absence, or insufficient amounts, of CCR7.

The findings by Gallego et al are relevant to ongoing clinical studies. AMD3100, also known as plerixafor, is a selective inhibitor of CXCR4, and is currently US Food and Drug Administration–approved for treatment of non-Hodgkin's lymphoma and multiple myeloma.[8] This drug is also under phase 1 study for WHIM patients (#NCT00967785), and preliminary results indicate that the drug ameliorates multiple aspects of that disease, including panleukopenia, wart burden, and frequency of papillomavirus-associated oropharyngeal squamous cell carcinoma.[9] It might be anticipated that AMD3100 treatment of *Cxcr4*$^{+/1013}$ mice would reverse their gain-of-function features, including the impaired migration of skin DCs to LNs. However, AMD3100 had little effect on skin DC migration in these animals. AMD3100 did, however, reduce DC migration in wild-type mice, confirming a previous report by Kabashima et al.[4] It is unclear why AMD3100 has no effect on skin DC migration in *Cxcr4*$^{+/1013}$ mice, but it is possible that WHIM syndrome patients are also resistant to at least some of the effects of AMD3100 on DC migration. Whether that turns out to have a beneficial, or deleterious, effect on adaptive immune responses in these patients remains to be seen.

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LYMPHOID NEOPLASIA

Comment on Mato et al, page 2817

Kinase inhibitors in CLL: drawing the roadmap

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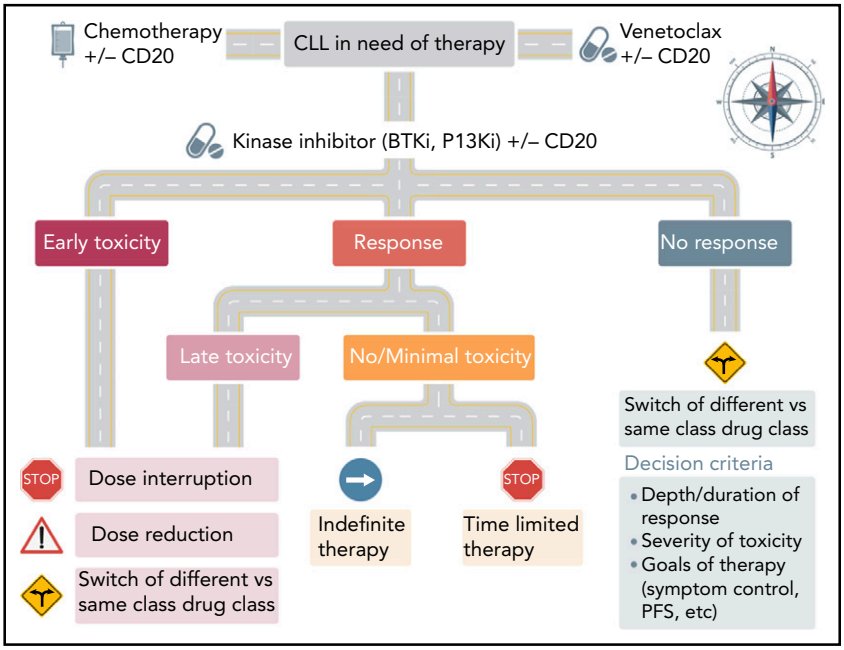
In this issue of *Blood*, Mato et al report the results of an open-label multicenter phase 2 study of the phosphatidylinositol 3-kinase (PI3K) inhibitor umbralisib in patients with chronic lymphocytic leukemia (CLL) who were intolerant of Bruton tyrosine kinase (BTK) or inhibitors they had received earlier.[1]

Over the last several years, several small-molecule kinase inhibitors (KIs) were approved in various indications across B-cell malignancies. Specifically, the integration of BTK inhibitors (BTKi's) and PI3K inhibitors (PI3Ki's) alone and in combination with anti-CD20 therapy into CLL treatment regimens resulted in a paradigm shift away from traditional chemotherapy-based backbones as preferred management. This shift resulted in improved outcomes across a broad swath of patients in nearly every measurable outcome, including overall survival (OS). Recently, long-term follow-up of registration-enabling studies for BTKi's and PI3Ki's were published. In untreated patients with CLL who were older than age 65 years, single-agent ibrutinib resulted in a 70% 5-year progression-free survival (PFS) and an 83% 5-year OS.[2] Mature reports of idelalisib plus rituximab in relapsed CLL also demonstrated a persistent PFS benefit over rituximab alone.[3] Not surprisingly, the phenomenal activity observed in these and other early studies resulted in rapid development of next-generation BTKi's and PI3Ki's with slightly different mechanisms of action, target specificity, method of delivery, and pharmacokinetics.

However, as experience with prolonged exposure to these first agents grew, it became clear that each drug was associated with rare, but unique and often serious adverse events (AEs). In addition to well-characterized rash and low-grade bleeding and bruising, ibrutinib is also associated with an increasing risk of atrial fibrillation. In



Roadmap for use of KIs in CLL. The decision to continue or switch KI therapy in CLL is based on the severity and timing of previous toxicity and quality of response. In patients with early toxicity or responding patients who have delayed non–life-threatening AEs, consideration can be given to dose interruption or reduction. In patients who progress or develop severe or chronic toxicity, alternate class or alternate target inhibitor should be considered.

a pooled analysis of more than 1500 patients treated with ibrutinib from 4 large phase 3 studies, the agent was associated with a low but continuous rate of arrhythmia. Although only 5.3% of patients experienced atrial fibrillation in the first 6 months, the cumulative incidence increased to 13.8% after 36 months of drug exposure.[4] Idelalisib has been associated with rare but occasionally severe autoimmune-related colitis, pneumonitis, and risk of infections. Interim safety analyses of 3 phase 3 studies in patients with previously untreated CLL and indolent B-cell non-Hodgkin lymphoma were halted because of excess deaths and serious AEs, including opportunistic infections, among patients in the groups treated with idelalisib.[5] Perhaps not surprisingly, toxicity (not progression!) has become the most common reason for discontinuation of tyrosine kinase inhibitors in clinical practice.[6] Hence, as second-generation BTKi's and PI3Ki's entered into clinical studies, there was great hope that differing mechanisms of action and/or mode of delivery would result in greater tolerability with equal or even improved efficacy.

Umbralisib is an oral PI3Kδ inhibitor which also inhibits CK1ε. Unlike previous PI3Ki's, it is not metabolized through the CYP pathway and has potentially higher selectivity for the δ isoform of PI3K, thought to be the primary drug target in CLL. Recently, a randomized phase 3 study of umbralisib plus ublituximab compared with obinutuzumab plus chlorambucil in untreated and relapsed CLL was closed after an independent review panel determined that the umbralisib combination induced a statistically significant improvement in PFS ($P < .0001$).[7]

Mato et al report the results of one of the first studies to prospectively explore the ability to switch between KIs (either within or across classes) in patients who exhibited intolerance to a previous KI. The study enrolled 51 previously treated CLL patients (44 had previous exposure to BTKi's and 7 had previous exposure to PI3Ki's). At study entry, patients were given single-agent umbralisib until disease progression or unacceptable toxicity. Overall, the strategy seemed to be effective, with a median PFS of 23.5 months. Importantly, the median duration while receiving therapy was longer with umbralisib than with previous KIs. Although rare AEs such as pneumonitis and colitis were observed, only 8 patients (16%) had dose reductions and only 12% discontinued umbralisib because of toxicity. Although these findings suggest that umbralisib has a better tolerability profile than other KIs, true comparison is difficult without a head-to-head study.

The Mato et al study is the first to suggest that switching between KIs with different mechanisms of action is effective and safe in CLL. It also supports the growing understanding that until combination studies mature, the majority of emerging targeted agents in CLL will likely be used in series. Despite these encouraging results, several questions remain. What is the ideal roadmap for sequencing KIs or other targeted agents? Is dose or schedule reduction, interruption, or time-limited therapy an alternative to switching agents (especially in responding patients)?

As next-generation KIs with more tolerable toxicity profiles become broadly available, it is likely that more patients will receive effective therapy and remain on it longer. Several ongoing studies are also exploring innovative dosing schedules as well as time-limited therapy in patients who achieve minimal residual disease negativity. Until these studies are complete, preliminary evidence from real-world studies suggests that some patients can be successfully re-challenged after dose interruption or reduction without changing agents.[5,6] Of course, the decision to resume dosing should be carefully considered and must weigh the severity and duration of previous toxicity against the magnitude of previous response and the immediate risk of CLL to the patient's long term outcome (see figure). For patients in whom re-exposure is attempted, close multidisciplinary monitoring is recommended. Although these decisions currently represent a therapeutic challenge, they also exemplify the bright and dynamic future of CLL therapy, in which more and more clinicians will have the luxury of choice between several safe and effective options to improve the outcomes of CLL patients in their care.

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MYELOID NEOPLASIA

Comment on Duchmann et al, page 2827

What can Heraclitus tell us about AML?

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In this issue of *Blood*, Duchmann et al demonstrate the influence of comutations on the prognostic significance of isocitrate dehydrogenase (*IDH*) mutations in adult patients with newly diagnosed acute myeloid leukemia (AML) treated with intensive chemotherapy (IC) and followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT) in eligible patients.[1]

In *IDH1*- and *IDH2R140*-mutated AML treated with IC, the cooccurrence of an *NPM1* mutation is the most important prognostic factor with favorable influence on overall survival (OS). *IDH*-mutated AML with additional poor prognostic features, according to the scoring system of the European LeukemiaNET (ELN 2010), benefits from allo-HSCT in first complete remission (CR1).

AML is now regarded as a group of hematopoietic neoplasms that are characterized by a sequence of genetic alterations which, in their complex hierarchical architecture, influence AML pathogenesis and are also responsible for heterogeneity in clinical presentation and outcome.[2] Recent advances have resulted in the characterization of distinct molecular groups that predict the individual likelihood of a patient to respond to treatment, risk of disease progression, relapse, and death.[3] Some of these genetic subclasses have already been included in the 2016 World Health Organization revised classification of AML subgroups, namely mutations of *NPM1*, *CEBPα*, and *RUNX1*.[4] Mutations of *IDH1* and *IDH2* are not among these subclass-defining mutations.

Point mutations in *IDH1* and *IDH2* genes are rather common in adult AML, present in 7% to 14% and 8% to 19% of patients, respectively.[2] Mutated enzymes produce excess amounts of an oncometabolite, D-2-hydroxglutarate with transforming activity. Oral inhibitors of mutant IDH1 and IDH2 enzymes have been developed and recently approved by the US Food and Drug Administration (FDA) as single agents for the treatment of relapsed/refractory AML with mutated *IDH1/2* and for newly diagnosed AML with mutated *IDH1*. Randomized trials with a combination of IDH inhibitors and IC in newly diagnosed AML are ongoing. Therefore, an improved definition of the genetic risk classification of each *IDH* mutation subtype is particularly relevant.

Although they share a common oncogenic mechanism, the most common *IDH* mutation subtypes (*IDH1R132*, *IDH2R140*, *IDH2R172*) have different landscapes of cooccurring mutations that impact prognosis and response to treatment.[3,5,6] Thus far, risk stratification of AML patients carrying *IDH* mutations and undergoing intensive induction chemotherapy has been difficult, producing conflicting results.[7] Ergo, *IDH* mutations do not play a role in the ELN 2010 and ELN 2017 scoring systems.[4,8] This retrospective analysis of 3 prospective clinical trials of the Acute Leukemia French Association (ALFA) looked at the prognostic impact of clinical and genetic covariates and the outcome of allo-HSCT in a large cohort of 319 newly diagnosed *IDH*-mutated AML patients. Apart from conventional cytogenetics, the molecular genetic analysis focused on the 37 genes overlapping in the 3 studies. The 2 major conclusions are that the presence of an *NPM1* mutation and a normal karyotype defined a subgroup with better OS, whereas in patients with nonfavorable ELN 2010 scores, allogeneic stem cell transplantation (allo-HSCT) improved both OS and disease-free survival.

What do the data tell us and what are the limitations? The study adds a considerable amount of data on the impact of IDH subtypes and comutations and serves as a baseline for the clinical trials with IDH inhibitors. First, the IDH subtypes present in different biological ways and have different outcome after IC and therefore should be looked at separately in future clinical trials. The presence of a concurrent *NPM1* mutation is the main prognostic factor for a good response to IC in *IDH1*- and *IDH2R140*-mutated AML. This could serve as an argument to stratify IDH-mutated AML in the ongoing or planned clinical trials with IC and IDH inhibitors according to the *NPM1* mutation status. However, because this behavior is only seen in patients with wild-type *DNMT3A*, as has been previously reported for the *NPM1/DNMT3A/FLT3*–internal tandem duplication triple mutation,[3] the stratification rules might need to become more complex the more we learn about these interactions. In addition, the implementation of IDH inhibitors in our treatment strategies might influence the prognostic impact of certain mutations. Other new drugs like venetoclax also have surprisingly good activity against *IDH*-mutated leukemic blast cells in vitro.

The present study shows that patients with nonfavorable ELN 2010 *IDH*-mutated AML did benefit from allo-HSCT in CR1. Thus, the presence of *IDH* mutations did not change the risk stratification and should not alter the current treatment recommendations. Again, the situation will have to be reevaluated after the integration of the IDH inhibitors, or drugs like venetoclax,