be used for timely treatment changes as soon as resistance develops.

In the future, it will be essential to continue exploring the possibility of in vivo coupling of B-BiTEs with circulating antibodies. This is particularly relevant for patients with autoimmune disease, as well as those with autoantibodies of unknown clinical significance. Moreover, all patients with MM present with elevated amounts of mAbs; although the antigen specificity of these paraproteins remains poorly understood, it has been proposed that chronic antigen stimulation causes monoclonal gammopathy of undetermined significance,[4] the premalignant, precursor stage of MM. The possibility that these antibodies react to chronic viruses[5] or self-antigens[6] should be considered when evaluating the safety of this treatment. Finally, the authors did not observe regulatory T-cell (Treg) activation, despite the ability of Tregs to be activated by CD3. This finding deserves further exploration, especially as preliminary results suggest that Tregs may limit the activity of the bispecific antibody teclistamab in MM.[7] These concerns notwithstanding, further developments of this therapeutic strategy could provide clinicians with an arsenal of flexible options for T-cell (and NK-cell) redirecting therapy and could benefit the care of patients with MM.

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LYMPHOID NEOPLASIA

Comment on Kim et al, page 1806

Unraveling *KMT2A*-rearranged ALL

Shai Shimony[1,2] and Marlise R. Luskin[1] | [1]Dana-Farber Cancer Institute and [2]Rabin Medical Center and Tel Aviv Faculty of Medicine

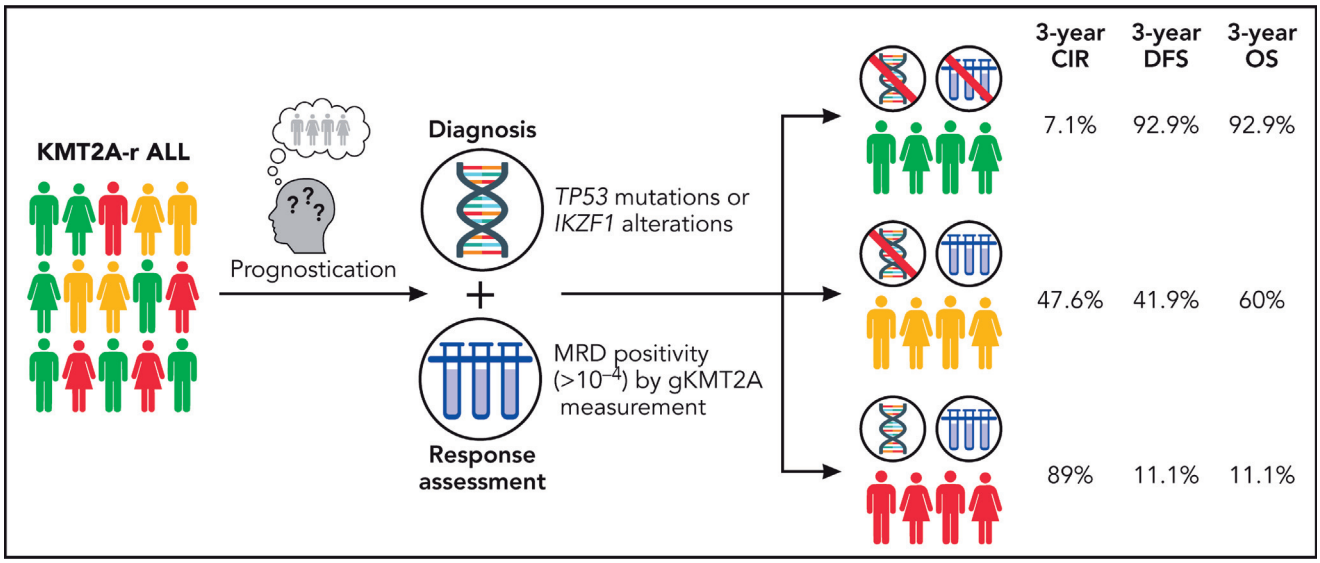
In this issue of *Blood*, Kim et al[1] from the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) take us one giant leap forward in our understanding of adult *KMT2A*-rearranged (*KMT2A*-r) B-cell precursor acute lymphoblastic leukemia (B-ALL). For the first time, they demonstrate the ability to risk stratify young adults within this high-risk group and identify patients with *KMT2A*-r B-ALL with outstanding outcomes when treated with intensive, pediatric-inspired chemotherapy, even *without* allogeneic hematopoietic stem cell transplant (HSCT).

We have come a long way since 1948 when Sidney Farber announced transient responses in 5 children treated with the folic acid antagonist aminopterin.[2] What has followed is 75 years of worldwide, pediatrician-led collaboration to improve outcomes in ALL. We are fortunate that now >90% of children diagnosed with ALL in resourced settings are cured with modern, risk-adapted chemotherapy.[3] Younger adults treated with intensive, pediatric-style asparaginase-based chemotherapy are also now frequently cured, almost (although not quite) as often as children.[4] The use of HSCT is typically reserved for high-risk patients (by various definitions) or those not achieving an optimal early response.[5]

Still, *KMT2A*-r ALL remains a feared subtype of ALL with historically dismal outcomes in infants,[6] as well as adults.[7] Indeed, relapsed *KMT2A*-r ALL is a dreaded occurrence given infrequent and fleeting responses to available immunotherapy (blinatumomab, inotuzumab ozogamicin, and chimeric antigen receptor T cells) and risk of lineage switch. Thus, most adult groups recommend HSCT in first complete remission (CR1) for eligible patients based on the presumption of consistently adverse disease biology. Until now, there have been no data to help a clinician further risk stratify a patient or support a non-HSCT approach.

In this context, the GRAALL investigators studied 141 adult patients with *KMT2A*-r ALL (median age, 41 years; range, 18-59 years; 12.9% of overall GRAALL cohort) treated on 3 successive GRAALL trials of intensive pediatric-inspired chemotherapy (GRAALL-2003, GRAALL-2005, and GRAALL-2014) with the goal of identifying factors associated with clinical outcomes. The *KMT2A*-r patients in the GRAALL cohort were, as expected, characterized by high-risk clinical features (older age and higher white blood cell count) but almost universally achieved CR1 with a single induction with a 5-year cumulative incidence of relapse (CIR) of 40.7% and a 5-year overall survival (OS) of 53.3%. The authors then demonstrated that patients with *KMT2A*-r ALL could be risk stratified using genetic profiling and measurable residual disease (MRD) assessment.

Regarding genetics, like infant *KMT2A*-r ALL, there was a low rate of additional mutations, with the most frequent being subclonal mutations in *RAS* and receptor



Prognostication model for *KMT2A*-rearranged (*KMT2A*-r) acute lymphoblastic leukemia (ALL). CIR, cumulative incidence of relapse; DFS, disease-free survival; g*KMT2A*, genomic fusion assay for *KMT2A*; MRD, measurable residual disease; OS, overall survival. Professional illustration by Patrick Lane, ScEYEnce Studios.

tyrosine kinase genes (38%). Less frequent, but notably prognostic, were mutations in *TP53* (14%) and *IKZF1* deletions (8%). Patients with any of these high-risk mutations had a higher 5-year CIR (69.3% vs 36.2%; $P = .001$) and a lower 5-year OS (28.1% vs 60.7%; $P = .006$). The statistics were most robust for the more-frequent *TP53*-mutated patients, all of whom had aggressive disease biology (ie, relapsing within 6 months). Regarding MRD assessment, monitoring using a *KMT2A* genomic fusion assay, rather than tracking Ig/T-cell receptor rearrangements, was more reliable (similar to infant *KMT2A*-r ALL), as the latter are either absent at diagnosis or at risk for clonal evolution. Remarkably, patients with early *KMT2A*-based MRD response (of note, all lacking the aforementioned high-risk genetics at diagnosis) had superb outcomes (3-year CIR, 7.1%; and OS, 92.9%).

Translating their findings onto a clinically useful paradigm, the GRAALL investigators created a classifier combining molecular profiling at diagnosis (if no high-risk mutations: Onco$^-$; if high-risk mutations: Onco$^+$) and MRD to create 3 groups with distinct outcomes: Onco$^-$/MRD$^-$, Onco$^-$/MRD$^+$, and Onco$^+$/MRD$^+$, which were associated with starkly divergent 3-year CIR (7.1%, 47.6%, and 88.9%, respectively), disease-free survival (92.9%, 41.9%, and 11.1%, respectively), and OS (92.9%, 60.0%, and 11.1%, respectively) rates (see figure). Notably, the excellent findings of the MRD$^-$ group occurred in the absence of HSCT in CR1, as the GRAALL-14 trial did not allocate *KMT2A*-r patients to HSCT if they achieved MRD$^-$ CR.

Thus, in the context of younger adult patients receiving intensive pediatric-type chemotherapy, the discovery of a *KMT2A*-r may not warrant automatic dismay. Rather, with risk stratification by molecular profiling at diagnosis and MRD monitoring, risk-adapted therapy appeared beneficial, akin to the dynamic approach employed for other subtypes of Philadelphia chromosome–negative ALL and Philadelphia chromosome–positive ALL.[5] This promises to allow intensively treated adults with *KMT2A*-r ALL without mutant *TP53* or *IKZF1* deletion and an optimal response to avoid the toxicity of (typically total body irradiation-based) myeloablative HSCT.

So, what next? The classifier created by the GRAALL investigators will ideally be studied in additional large ALL cohorts, including among children and young adults treated with other intensive asparaginase-based pediatric regimens, as well as among older patients treated with non–asparaginase-based treatment with or without novel agents. More important, as novel treatment approaches for *KMT2A*-r ALL, including blinatumomab consolidation[8] and menin inhibitors,[9] are being developed with the potential to modify the outcomes of higher-risk patients, their effect according to the classifier risk groups will need to be studied. Finally, the ability of therapeutic intensification with HSCT to improve cure in higher-risk patients needs further evaluation. Given the rarity of *KMT2A*-r ALL (5%-10% of noninfant childhood and adult ALL), the leukemia community will need to cooperate in an international *KMT2A*-r program to speed ascertainment of data and clinical understanding as the therapeutic landscape rapidly evolves.

Philadelphia chromosome–positive B-ALL, once a similarly feared ALL subtype, has been transformed by better treatments as well as more precise monitoring and refined risk stratification schemes, changing from an adverse to a nonadverse subtype.[10] Can we dare to imagine the same for *KMT2A*-r ALL? Basic, translational, and clinical research in ALL has taken us to the (metaphorical) moon over the past 75 years. Now, let's go to Mars!

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MYELOID NEOPLASIA

Comment on Papadopoulos et al, page 1818

Hidden conformational codes

Kaosheng Lv[1] and Wei Tong[2,3] | [1]Southern University of Science and Technology; [2]Children's Hospital of Philadelphia; and [3]Perelman School of Medicine at the University of Pennsylvania

In this issue of *Blood*, Papadopoulos et al[1] reveal that oncogenic JAK2V617F elicits a unique pattern of active human thrombopoietin receptor (hTpoR) conformations distinct from those induced by its cognate ligand thrombopoietin (Tpo). These results point to a new therapeutic strategy of targeting JAK2V617F-specific interface with hTpoRs to eliminate pathologic JAK2V617F$^+$ myeloproliferative neoplasms (MPNs) without impacting wild-type (WT) cells.

The TpoR is important for megakaryocyte and platelet development as well as hematopoietic stem cell (HSC) expansion.[2,3] TpoR adopts different conformations and interfaces after dimerization to modulate the activation states in response to its cognate ligand Tpo or small-molecule agonist eltrombopag.[4] JAK2 is the critical kinase for stabilizing TpoR dimers and activating downstream signaling cascade.

Activating mutations in TpoR (W515K/L and S505N), JAK2 (V617F), and calreticulin are found at high frequencies in MPNs.[5] Mechanistically, these driver mutations act through TpoR and converge on JAK-STAT signaling in all subtypes of MPNs,[6] pointing to the central role of TpoR and JAK2 in the pathogenesis of MPN. Although JAK inhibitors (JAKi) (eg, ruxolitinib) alleviate disease-associated symptoms in MPN, the allele burden of JAK2V617F is only mildly reduced in most patients, partly due to JAK2V617F$^+$. HSCs reenter dormancy and therefore are insensitive to JAKi[7] or heterodimeric JAK1 reactivation.[8] One disadvantage of JAKi is the side effects caused by its inability to discriminate between oncogenic JAK2V617F and its WT counterpart. Thus, the exploration of novel therapeutic strategies by targeting the TpoR/JAK2 axis requires a better understanding of JAK2V617F/TpoR activation and signaling.

Despite the advance in our understanding of the TpoR/JAK2 signaling, the deeper structural basis regarding the transmembrane (TM) and juxtamembrane domain for their activation remains elusive. To overcome this barrier, Constantinescu and colleagues devised an alternative strategy to impose 7 dimeric orientations of a cytokine receptor via the replacement of the extracellular domain with an amphipathic coiled-coil domain.[9] By applying this strategy to erythropoietin receptor (EpoR), they identified 3 distinct conformations of EpoR during no, partial, and full activation, respectively.[9] In the case of mouse TpoR (mTpoR), they found that several different conformations are able to mediate its constitutive activation and induce specific MPN phenotypes.[10] These investigations indicate that a single receptor can transmit different types or strengths of downstream signaling by fine-tuning its conformation. However, the scope of the studies previously mentioned was limited to studying the receptor with JAK2 WT without considering the potential effect of oncogenic JAK2V617F. Moreover, the mechanism obtained from mTpoR cannot be assumed to be the same in hTpoRs because mTpoRs have notable amino acid differences in the cytoplasmic domain—for example, the key eltrombopag binding site in the hTpoR TM domain, H499, is absent in the mTpoR.

Papadopoulos et al further explored the activation pattern of hTpoR under physiological and pathological conditions (see figure). By applying the aforementioned strategy to hTpoR, they found that active hTpoRs adopt a distinct conformational pattern different from that of mTpoRs, attributable to the difference of 2 amino acids, G503 and H499. Next, they tested the downstream signaling spectrum of hTpoRs. Unlike EpoRs and mTpoRs, where different conformations selectively favor one signaling over another, all active hTpoR conformations appear to unbiasedly stimulate the same downstream signaling in the presence of either JAK2 WT or V617F. It is noteworthy that for a specific hTpoR conformation, JAK2V617F and WT elicit different strengths of STAT phosphorylation, and this discrepancy is only observed in hTpoR, but not mTpoR. More importantly, the authors compared