therapeutically? Because the dynamics was only observed in artificial culture conditions, even though similar dynamics likely occur in vivo, investigating such dynamics in vivo awaits more sophisticated tools. On a fundamental level, a pressing question that is not addressed in the report by Kull et al is what determines NF-κB dynamics in response to the same signals. The authors described observations, such as larger nuclear area or shorter cell cycle, in association with specific NF-κB dynamics; is this only an association or is there a specific mechanism linking them? Last, NF-κB is only one of several common oscillating dynamics responding rapidly to environmental signals. In this regard, the role of ERK dynamics in cell fate determination has been widely reported, including in hematopoietic stem and progenitors.[9,10] Because oscillating behavior inherently implies or measures time, integrating oscillating dynamics could be a general theme for how individual cells interprets time, so that what they are now and what they become next could be coordinated in sync with the need of the tissue or the organism.

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REFERENCES

1. Kull T, Wehling A, Etzrodt M, et al. NfκB signaling dynamics and their target genes differ between mouse blood cell types and induce distinct cell behavior. *Blood.* 2022; 140(2):99-111.

2. Hérault A, Binnewies M, Leong S, et al. Myeloid progenitor cluster formation drives emergency and leukaemic myelopoiesis. *Nature.* 2017;544(7648):53-58.

3. Rekhtman N, Radparvar F, Evans T, Skoultchi AI. Direct interaction of hematopoietic transcription factors PU.1 and GATA-1: functional antagonism in erythroid cells. *Genes Dev.* 1999;13(11):1398-1411.

4. Olsson A, Venkatasubramanian M, Chaudhri VK, et al. Single-cell analysis of mixed-lineage states leading to a binary cell fate choice. *Nature.* 2016;537(7622):698-702.

5. Haas S, Trumpp A, Milsom MD. Causes and consequences of hematopoietic stem cell heterogeneity. *Cell Stem Cell.* 2018;22(5): 627-638.

6. Puram RV, Kowalczyk MS, de Boer CG, et al. Core circadian clock genes regulate leukemia stem cells in AML. *Cell.* 2016;165 (2):303-316.

7. Eisenstein M. Rejuvenation by controlled reprogramming is the latest gambit in anti-aging. *Nat Biotechnol.* 2022;40(2):144-146.

8. Pietras EM. Inflammation: a key regulator of hematopoietic stem cell fate in health and disease. *Blood.* 2017;130(15):1693-1698.

9. Lavoie H, Gagnon J, Therrien M. ERK signalling: a master regulator of cell behaviour, life and fate. *Nat Rev Mol Cell Biol.* 2020;21(10):607-632.

10. Wang W, Zhang Y, Dettinger P, et al. Cytokine combinations for human blood stem cell expansion induce cell-type- and cytokine-specific signaling dynamics. *Blood.* 2021;138(10):847-857.

LYMPHOID NEOPLASIA

Ibrutinib frontline in young patients with CLL

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In this issue of *Blood*, Shanafelt et al[1] confirm the continued superiority of ibrutinib plus rituximab (IR), compared with the prior standard treatment, fludarabine, cyclophosphamide, and rituximab (FCR), for fit patients with chronic lymphocytic leukemia (CLL). In addition, they report relevant data on the tolerability of continuous treatment with BTK inhibitor.

More than 17 years ago, the FCR chemo-immunotherapy regimen was developed by the MD Anderson Center (Houston, TX)[2] and was later shown to be superior to chemotherapy alone.[3] Later, extended follow-up data showed that this regimen in younger, fit patients had the potential for long-lasting disease control, possibly even cure, in a subgroup of patients with favorable prognostic profile.[4,5] In contrast to FCR, chemoimmunotherapies based on less-intensive chemotherapy backbones, such as chlorambucil or bendamustine, did not show similar long-lasting remissions in more elderly and less fit patients. BTK inhibitors, alone or in combination with anti-CD20 antibodies, had been shown to be superior to those less intensive treatment regimens in elderly or unfit patients with CLL.[6,7]

In the E1912 study, the ECOG-ACRIN study group reported that, at a median of 34 months, the IR regimen was superior to FCR. Now, a follow-up of nearly 6 years clearly confirms the superiority of IR with respect to progression-free survival (PFS) (5-year PFS rates for IR, 78% and for FCR, 51%; HR [hazard ratio], 0.37; 95% confidence interval [CI], 0.27-0.61; $P < .0001$). Notably, even the subgroup of patients with mutated immunoglobulin heavy chain (IGHV) status, which benefitted most from the FCR regimen,[4,5] had an HR of 0.27 (95% CI, 0.1-0.62) for PFS. Although overall survival (OS) for the IR-treated group was still superior with longer follow-up, the difference was less than in the previous report. A subgroup analysis for OS showed that only patients with unmutated IGHV status benefited from IR, a finding limited by the reduced power of this secondary analysis (HR 0.35 for OS in patients without mutated IGHV (95% CI, 0.15-0.80) vs HR 0.72 in those with a mutation (95% CI, 0.15-3.47). The decreasing difference in OS may be related to greater use of targeted agents in relapsed disease than during the first study.[8] However, because data for relapse treatment were available only for patients dying of CLL or Richter transformation (see supplemental Table 3A in Shanafelt et al), this hypothesis cannot be confirmed by complete data analysis of all salvage therapies.

The outcome of patients who discontinued ibrutinib treatment because of adverse events was also presented. These data are highly relevant for clinical management. Seventy-seven patients (21.9% of all patients from the IR arm) discontinued BTK inhibitor therapy after a median time of 25.9 months, because of adverse events or complications. The update shows that the median time from ibrutinib discontinuation to disease progression was 25 months. Although the difference was not statistically significant, the tendency was for longer duration of ibrutinib therapy, particularly treatment exceeding 1 year, to result in longer disease-free survival after treatment discontinuation. Moreover, despite the difference in treatment duration, the IR

arm was associated with a lower rate of grade 3 and more treatment-related adverse events compared with the FCR arm (73.0% vs 83.5%).

The results of the E1912 trial have to been seen in context with those of the FLAIR study, which was presented at the ASH 2021 meeting.[9] This phase 3 trial by the UK CLL study group also compared FCR to IR, but the average age of the patients was older (median age, 63 vs 58 years in the E1912 study). Interestingly, no difference in OS was observed for the FLAIR study, despite a significant difference in PFS with an HR of 0.44 (95% CI, 0.32-0.60) after a median observation time of 52.7 months.[9] As Shanafelt and colleagues report, an increasing incidence of cardiac toxicity in a more elderly patient population in the FLAIR study, with 9 lethal cardiac events vs only 1 in the E1912 study, may be one of several reasons responsible for the lack of difference in OS.

Altogether, the update of the E1912 study confirmed that the safe and very efficacious administration of IR in younger patients with CLL is superior to FCR, independent of IGHV status. How continuous therapy compares to time-limited targeted therapies such as venetoclax plus obinutuzumab or venetoclax plus BTK inhibitor will be shown by currently ongoing phase 3 trials.

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REFERENCES

1. Shanafelt TD, Wang XV, Hanson CA, et al. Long-term outcomes for ibrutinib–rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. *Blood.* 2022;140(2): 112-120.

2. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol.* 2005; 23(18):4079-4088.

3. Hallek M, Fischer K, Fingerle-Rowson G, et al; German Chronic Lymphocytic Leukaemia Study Group. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet.* 2010;376(9747):1164-1174.

4. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term

disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood.* 2016;127(3): 303-309.

5. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood.* 2016;127(2):208-215.

6. Burger JA, Robak T, Demirkan F, et al. Up to 6.5 years (median 4 years) follow-up of first-line ibruinib in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma and high-risk genomic features: Integrated analysis of two phase 3 studies Leuk Lymphoma 2022; 11; 1–12

7. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for

treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet.* 2020; 395(10232):1278-1291.

8. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med.* 2019;381(5):432-443.

9. Hillmen P, Pitchford A, Bloor A, et al. Ibrutinib plus rituximab is superior to FCR in previously untreated CLL: results of the Phase III NCRI FLAIR Trial B [abstract]. *Blood.* 2021; 138(suppl 1). Abstract 642.

PLATELETS AND THROMBOPOIESIS

Comment on Kaiser et al, page 121

GPIIb/IIIa-GPVI–commanded platelet patrol

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In this issue of *Blood*, Kaiser et al[1] reveal how the reparative process is initiated by ceaselessly vigilant patrolling platelets that turn procoagulant and instigate hemostatic plug formation to seal endothelial gaps in the wake of transmigrating leukocytes.

Platelets as keepers of vascular integrity can prevent hemorrhage in the dense microvascular beds of lungs, gastrointestinal tract, and skin during nonsterile inflammation.[2] Whether the molecular mediators of primary hemostasis overlap with or are distinct from those mounting inflammatory hemostasis is an absorbing yet unresolved enigma. Kaiser et al have capitalized on their previous findings, which describe immune-competent migratory platelets[3] that sense vascular breaches (see figure).[4] An extensive and elegantly performed series of in vitro and in vivo experiments after lipopolysaccharide (LPS)-induced inflammation that affected the mesenteric and pulmonary vasculature shows that migrating platelets on the watch are arrested on collagen to drive inflammatory hemostasis, involving costimulatory cues from glycoprotein IIb/IIIa (GPIIb/IIIa)–mediated outside-in-signaling and GPVI. While providing a translational perspective the investigators have further verified that simultaneous pharmacologic targeting of GPIIb/IIIa and GPVI, also anticoagulants in clinical practice (argatroban, enoxaparin, rivaroxaban) may aggravate

alveolar hemorrhage. This is indeed a matter of concern, especially in immuno-thrombotic diseases such as SARS-CoV-2 (COVID-19), in which lungs are the acute inflammatory hotspots. The procoagulant platelets[5] in the circulation of COVID-19 patients provoke a hyper-coagulatory and prothrombotic disposition which worsens prognosis and thus requires therapeutic or prophylactic administration of anticoagulants.

It is well known that platelets seal endothelial breaks that result from leukocyte extravasation to prevent inflammatory hemorrhage because thrombocytopenia aggravates dermal and alveolar bleeding; however, $\beta3\text{-}integrin^{-/-}$ and $Fc\gamma R^{-/-}$ mice[2] are spared. The study by Kaiser et al revisits the old chapters on this subject to fill in the gaps in our understanding regarding the mechanistic drivers of inflammatory hemostasis. Their investigation delineates the sequence of events whereby costimulatory mechanosignals from GPIIb/IIIa-GPVI[6,7] arrest migratory platelets on exposed subendothelial collagen and eventually transform them into a procoagulant ballooning phenotype[8]