systemic gram-negative bacterial infection. These observations, however, were far from predictable because cells of hematopoietic origin (eg, macrophages, dendritic cells) are typically considered front-line sensors of extracellular pathogens and are potent mediators of TLR signals, with numerous critical roles in regulating the interplay between innate and adaptive immune responses. Moreover, hematopoietic progenitors express TLRs, which suggested a potential direct mechanism of pathogen sensing to activate emergency hematopoiesis. Evidence herein argues strongly in favor of the importance of indirect sensing via the endothelium for response to systemic bacterial challenge.1,3

Endothelium for response to systemic infection may trigger G-CSF and/or other granulopoietic cytokine production by endothelial and/or hematopoietic populations to induce emergency granulopoiesis. One hopes the results here will prompt further investigation into cell populations and mechanisms that regulate physiologically relevant production of hematopoietic growth factors in response to local and systemic stressors (eg, infection, chemotherapy) as well as the primary sources of these molecules in steady state. Regardless, the fundamental idea that the vasculature can sense and respond to systemically delivered TLR agonists will no doubt shape our view of how other potential danger signals, such as extracellular nucleic acids or cell damage molecules, might affect hematopoiesis. Because these mediators are released in numerous disease states, including inflammation and cancer, and emergency hematopoietic responses might in turn influence disease outcomes (eg, production of inflammatory or immunosuppressive populations), understanding roles for endothelial cell–derived hematopoietic factors in different disease or pathogen-elicited scenarios is of critical importance. Both the vasculature and the marrow are dispersed throughout the body, potentially receiving not only systemically delivered messages, but also local tweets that could reveal important changes in environmental conditions warranting emergency hematopoietic responses. Our ability to recognize and detect such signals is clearly evident in healthy individuals in vivo. This capacity needs to be correspondingly enhanced in the laboratory to understand the full spectrum of microbial messaging to the marrow.

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CLINICAL TRIALS & OBSERVATIONS
Comment on Moorman et al, page 1434

The clinical path to integrated genomics in ALL

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In this issue of Blood, Moorman et al show that most good-risk patients can now be classified robustly by integrating the information from prevalent copy-number alterations (CNAs) in relevant combinations and classical cytogenetic risk factors in acute lymphoblastic leukemia (ALL).1

ALL is a complex genetic disease that results from the combination of lesions in genes involved in the regulation of hematopoiesis, lymphoid differentiation, cell cycle, and proliferation. High-resolution genetic profiling of ALL reveals an increasing number of underlying mutations that modify the function of transcription factors, epigenetic regulators, or components of signaling pathways, among others. For decades, cytogeneticists have been aware of specific chromosomal translocations, some of which have been established as reliable risk factors (see figure). However, these genetic risk factors identify only some of the patients at risk. Most study groups therefore also include the assessment of minimal residual disease (MRD) during induction chemotherapy for risk stratification, a powerful approach that was pioneered by European study groups.3,4

The challenge is now to devise new approaches to translate the rapidly expanding knowledge of ALL genomics to the clinic in order to define better prognostic markers and specific druggable targets already at diagnosis. The most common submicroscopic genetic lesions include CNAs or sequence mutations of hematopoietic transcription factors, including PAX5, IKZF1, and EBF1; gene rearrangements leading to overexpression of the cytokine receptor component CRLF2; mutations in JAK1 and JAK2 kinases; and deletions of CDKN2A/B loci encoding the INK4/ARF tumor suppressor genes, to name representative examples. Several of these lesions have been associated with less favorable outcome (such as CDKN2A/CDKN2B and IKZF1 deletions and...
In the present study, Moorman et al took advantage of multiplex ligation-dependent probe amplification to detect the most frequent CNAs retrospectively in >1,600 patients treated in the ALL97/99 (n = 864) and UKALL2003 (n = 742) trials in order to establish constellations of CNAs that would be associated with outcome. Using ALL97/99 as a test cohort, they determined the prognostic relevance of different genetic constellations of recurrent CNAs and integrated the resulting CNAs into a group associated with outcome. In fact, good-risk patients with low MRD after induction chemotherapy had an overall survival of 99%. The immediate potential of this new approach for genetic classification is to identify favorable-risk patients who may qualify for treatment de-escalation. This will provide better tools for early interventions in clinical trials in an attempt to reduce toxicity.

In this study, Moorman et al took advantage of multiplex ligation-dependent probe amplification to detect the most frequent CNAs retrospectively in >1,600 patients treated in the ALL97/99 (n = 864) and UKALL2003 (n = 742) trials in order to establish constellations of CNAs that would be associated with outcome. Using ALL97/99 as a test cohort, they determined the prognostic relevance of different genetic constellations of recurrent CNAs and integrated the resulting 3 CNA risk groups with 3 cytogenetic risk groups to define 2 genetic risk groups. One strength of the study was that the classification was then validated using an independent cohort of patients treated in the UKALL2003 trial. Detection of CNA constellations that were associated with good risk enabled the reclassification of half of the patients with intermediate risk by cytogenetics into a group with favorable outcome (see figure). In fact, good-risk patients with low MRD after induction chemotherapy had an overall survival of 99%. The immediate potential of this new approach for genetic classification is to identify favorable-risk patients who may qualify for treatment de-escalation. This will provide better tools for early interventions in clinical trials in an attempt to reduce toxicity.

In conclusion, this study provides a widely applicable strategy to improve the definition of good-risk patients in ALL, which could also be implemented in countries with more limited access to high-end genomic technology. It represents an important step toward a more integrated use of biomedical data to guide ALL therapy. We can expect the rapid discovery of additional relevant ALL molecular phenotypes and the translation of this knowledge in interventional studies for the benefit of our patients.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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