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Bourquin, Jean-Pierre

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The clinical path to integrated genomics in ALL

Jean-Pierre Bourquin
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 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. 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 the 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).
Patients treated in the ALL97/99 (n = 3 CNA risk groups with 3 cytogenetic risk combinations and integrated the resulting the prognostic relevance of different CNA ALL97/99 as a test cohort, they determined to establish constellations of CNAs that most frequent CNAs retrospectively in dependent probe amplification patterns may lead to better options for clinical ABL1–association of for such a relevant combination is the strong emerged in the field. One of the first examples for such a relevant combination is the strong association of IKZF1 deletions with BCR-ABL1–positive ALL. Thus, the integration of multiple parameters to identify recurrent patterns may lead to better options for clinical management.

In the present study, Moorman et al took advantage of multiplex ligation-dependent probe amplification to detect the most frequent CNAs retrospectively in >1600 patients treated in the ALL97/99 (n = 864) and UKALL.2003 (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 CNA combinations 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 UKALL.2003 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.

This study illustrates at a very practical level the need for a systems-oriented analytical approach to personalize ALL treatment. On this path, we need to ingrate high-resolution genetic profiling with all other available layers of diagnostic and clinical information. For example, a subset of patients in the genetic good-risk group in this study remained MRD positive, which was associated with significantly more relapses but still an overall survival >90%, indicating that salvage was possible in most cases. The drivers of this de novo drug-resistance phenotype remain to be discovered and limit the currently available genetic classification. Similarly, the relevant genetic constellations of most high-risk patients who do not carry a prognostic cytogenetic marker (the so-called B-others) need systematic exploration. Of obvious importance among the B-other group is BCR-ABL1–like leukemia with a gene expression profile that resembles BCR-ABL1 ALL. Next-generation sequencing of representative cases revealed a wide range of genetic alterations leading to activation of cytokine-receptor and kinase signaling, involving ABL1, ABL2, EPOR, IL7R, JAK2, CSF1R, and PDGFRB, for example. Informative constellations also emerge here, such as the association with IKZF1 deletions, CDKN2A/B deletions, or P2RY8-CRLF2 fusions in patients with poor risk based on MRD.

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.

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REFERENCES