Old and New Prognostic Markers in Pediatric ALL

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Dear Readers,

Welcome to the spring issue of the IJHB, with a fresh bouquet of articles for you.

In this issue, Aydin et al. [1] compare conventional cytogenetics with FISH and RT-PCR testing for t(12;21)(p13;q22) in pediatric B-acute lymphoblastic leukemia (ALL) patients. This disease represents an outstanding example, together with APL and CML, of modern medicine's triumph over hematological malignancies using a combination of monitoring and risk-adapted therapeutic strategies [2]. The development and evolution of minimal residual disease (MRD) analysis by the relatively widely available flow cytometric techniques has rapidly made MRD the most decisive prognostic marker in ALL [3]. Standardization and availability remain pertinent issues in India, but the rate of dissemination of knowledge of the technique and its application remain enthralling examples of how quickly research is translating into better patient management.

On the molecular front in B-ALL, the importance of *bcr-abl* fusion, *MLL* rearrangements, DNA ploidy, t(12;21) and other prognostic markers is well-documented. Their occurrence in 80–90 % patients makes them widely applicable as well [2]. More recently, genome-wide analyses and high throughput sequencing have uncovered multiple key pathways frequently mutated in B-ALL. New ALL subtypes, most prominently, Philadelphia (Ph) chromosome-like ALL have been recognized based on abnormalities of lymphoid development, tumour suppression,

chromatin remodelling, intracellular kinases and cytokine receptors, and their downstream interactions with their ligands/regulators. High-risk Ph-like ALL is especially important since it is characterized by tyrosine kinase activation that can be inhibited with currently available pharmacological agents [4, 5]. Genomic profiling has also aided identification of inherited risk factors for leukaemia development including GATA3, IKZF1, CEBPE and CKDN2A [6].

FISH or PCR testing reveals the t(12;21) in ~25 % pediatric B-ALL, compared to only 2–3 % adults. The translocation is cryptic in the vast majority of cases, being undetectable by conventional karyotyping [7]. The resultant *ETV6-RUNX1* (previously called the *TEL-AML1*) fusion protein converts *RUNX1* from a transcriptional activator to a repressor. Since *RUNX1* is normally required for the expression of several hematopoiesis-specific genes as well as for lineage-specific transcription, its impact on leukemogenesis is profound. Clinically, *ETV6-RUNX1* is a good prognostic factor, found in children aged 1–10 years, with CD10 + ALL and characterized by late relapses with excellent chemosensitivity [2, 7]. From a laboratory perspective, as the Aydin paper [1] illustrates, FISH probes for the *ETV6/RUNX1* fusion also enable presumptive identification of aneuploidies of chromosomes 12 or 21 as well as *ETV6* or *RUNX1* deletions or amplifications. The poor prognostic intra-chromosomal amplification of chromosome 21 (iAMP21) is also detectable by this modality [7, 8].

In conclusion, the march continues towards better and more insightful prognostic tests for hematological malignancies. Upgrading our national laboratories to ensure that all patients with B-ALL receive timely, accurate and cost-effective testing should be a priority with the hematology community.

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