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A new subgroup of high-risk acute lymphoblastic leukaemia

Gene-expression profiling in childhood acute lymphoblastic leukaemia (ALL) was first done by Yeoh and colleagues¹ at St Jude Children's Research Hospital in Memphis, TN, USA, in 2002. Since then, many international paediatric ALL trial groups have incorporated genome-wide expression analyses into their studies.^{2–5} A key aim has been to identify novel predictors of outcome. However, due to the heterogeneity of childhood ALL and its rarity compared with most adult cancers, these studies have not identified robust and reproducible classifiers⁶ that are better than those in current clinical use: age, white blood-cell count, cytogenetics, morphological treatment response, and minimal-residual-disease monitoring.

In this issue of *The Lancet Oncology*, den Boer and colleagues⁷ describe a novel high-risk ALL subtype with a gene-expression profile that resembles Philadelphia chromosome-positive ALL—one that is not associated with any known risk factors. Philadelphia chromosome-positive ALL is a well recognised but rare poor-risk group of childhood ALL, characterised by abnormal signalling through the BCR-ABL1 fusion oncoprotein. Unlike many rare poor-risk groups, this new BCR-ABL1-like subtype comprises 15–20% of patients with ALL and includes many paediatric patients that will eventually relapse. If the subtype can be confirmed by other groups with different treatment protocols, this BCR-ABL1-like ALL will constitute a relevant and important study population for future clinical trials. In-vitro tests have shown that leukaemic blasts from these patients are significantly more resistant to asparaginase. The first clinical question to ask is whether it is possible to reduce relapses in this group by including patients in high-risk chemotherapy groups—ie, will the patients benefit from more intense treatment and can drug resistance be overcome in this subtype?

The report of a new ALL subtype is an exciting find; however, the story is still incomplete. Without established diagnostic criteria, it is impossible to allocate these patients to specific treatment groups within clinical trials. A key issue will be to develop and validate a gene-expression classifier that can prospectively identify these patients. In the meantime, other international ALL trial groups should interrogate their data sets (using the 110 probe set-based gene-expression classifier described in this paper) to confirm the clinical significance of this new ALL subtype in relation to other known risk factors. In particular, it is important to analyse the role of minimal-residual disease monitoring in these BCR-ABL1-like patients and check whether it is possible to identify patients at very high risk who might benefit from allogeneic stem-cell transplantation or those that might qualify for more experimental treatment strategies.

The biggest challenge will be to unravel the biology that underlies this novel subtype. High resolution, genome-wide single-nucleotide polymorphism arrays did not identify a genomic alteration common to all patients. However, about 80% of the alterations had deletions involving B-cell development genes, including the transcription factors IKZF1, TCF3, EBF1, and PAX5 as well as the pre-B-cell receptor surrogate light chain VPREB1. Den Boer and colleagues also describe IKZF1, PAX5, and VPREB1 deletions at high frequency in Philadelphia chromosome-positive ALL. Deletions in these genes are frequent in B-cell precursor ALL,^{8,9} and not restricted to Philadelphia chromosome-positive and BCR-ABL1-like ALL, so it is unlikely that these deletions are sufficient to explain the poor risk of this new ALL subtype and its similarities to Philadelphia chromosome-positive ALL. An important approach will be to identify any common signalling pathways that are activated in both subtypes and novel therapeutic targets that could be explored by future clinical trials. Identification of common pathways will raise questions such as: are these pathways activated by mutations, by epigenetic regulation, or is it only the high frequency of deletions of B-cell

development genes, in particular IKZF1, that make the two subtypes appear to be similar? Recent data by Mullighan and colleagues¹⁰ also demonstrate that alterations of IKZF1 are associated with a poor outcome and a BCR-ABL1-like transcription profile. Finally, is there heterogeneity in this subtype? At least some other poor-risk leukaemias, such as those with intrachromosomal amplification of chromosome 21 (iAMP21)¹¹ or the dicentric chromosome, dic(9;20), are included within this subtype, albeit at low frequency.

Despite unresolved questions, the study by den Boer and colleagues⁷ is important for showing how genome-wide expression arrays can help develop and improve molecular disease classification. This work will stimulate further research into the interesting new ALL subtype. Only once we understand the underlying biology, however, and can use this information for treatment allocation or the development of targeted therapy, will this subtype be relevant.

Josef Vormoor

Northern Institute for Cancer Research, Newcastle University, Sir James Spence Institute, Royal Victoria Infirmary, Newcastle upon Tyne, UK, NE1 4LP h.j.vormoor@ncl.ac.uk

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