EDITORIAL

Cytogenetics or MRD in B-cell ALL. Do both reign supreme?

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COMMENTARY

Cytogenetic aberrations were first recognized as dominant leukemia drivers by the late Dr. Janet Rowley 49 years ago [1]. Numerous cytogenetic aberrations have since been identified across all cancer types. In acute leukemia, karyotype evaluation became essential for classification and risk assessment. The prognostic effect of a specific cytogenetic aberration is best identified from large prospective clinical trials in which all patients are subject to the same treatment protocol. In adults with B-cell acute lymphoblastic leukemia (B-ALL), the current recognized risk factors were identified by the very large prospective study conducted by the Medical Research Council (MRC) in Britain and the Eastern Cooperative Oncology Group (ECOG) in the USA, UKALLXII/E2993 trial [2]. Initiated back in 1993, this trial identified patient age, laboratory results at presentation and depth of molecular response to induction therapy. At that time, only four cytogenetic aberrations (BCR-ABL1, KMT2A-AFF1, low hypodiploidy/near triploidy (HoTr), or complex karyotype) were noted as prognostic factors.

In recent years, large prospective pediatric B-ALL studies led to identification of several additional cytogenetic aberrations as well as gene deletions or copy number alterations (CNA) as important prognostic factors. Unfortunately, due to the small number of prospective large clinical trials in adults B- ALL, it was difficult to determine which of the aberrations identified as prognostic in the pediatric population are applicable also in adults. In this issue, Moorman and colleagues [3] elegantly suggest new cytogenetic-based risk categories for adults with B-ALL. Cytogenetic and copy number alterations (CNA) of 652 patients who participated in the UKALL14 study were analyzed. Looking back at the primary cytogenetic report of the UKALLXII/E2993trial, which was also led by Dr. Moorman as first author together with the late Dr Gordon DeWald, multiple aberrations were recorded although most were not associated with outcome and therefore at final analysis only four aberrations were recognized as prognostics. The risk model derived from the UKALLXII/E2993 trial includes genetic and clinical factors, selected by its statistical significance. The herein suggested new prognostic model addresses some limitations of the old model and incorporation of novel identified prognostic cytogenetic aberration. It also suggests a practical and simple approach for risk adapted clinical decisions in B-ALL.

The prognostic model derived from the UKALLXII/E2993 trial provides a host of risk factors with no hierarchy. In practice, based on the list of prognostic factors it is challenging to come up with a clear decision tree for a specific patient. For example, what is the actual relapse risk for a patient presenting with a specific combination of poor risk factors (age, WBC, poor risk cytogenetics) who achieves molecular remission (MRD negative) or of a patient presenting with no known poor risk factors but fails to achieve molecular response? Note that the cytogenetic prognostic aberrations recognized in the former model, do not cover all B-ALL cases. In the UKALL14 cohort, the prognostic aberrations were identified in only 340/652 (53%) patients.

Novel insights on the origin of ALL, development and classification, provide additional drive to re-evaluate the risk model in B-ALL. In the UKALLXII/E2993 study, both B- and T-ALL were considered as one disease and were included in the same cytogenetic analysis. However, not only are novel therapies targeting B-ALL and T-ALL separately, they are now recognized as discrete diseases with different driver and expression profiles.

Fortunately, significant progress in our understanding of B-ALL classification and risk prediction was achieved by leukemia pediatricians. A laborious and determined effort to reveal the underlying drivers of pediatric high-risk Ph-like group successfully identified two groups of aberrations, those involved in BCR-ABL and those in JAK2 activation [4].

The statistical methodology selected for risk factor identification in UKALLXII/E2993, namely multivariate analysis, meant that although patients with involved translocations such as KMT2A (previously called MLL) were identified with poor prognosis, its association with older age and high white blood cell count at presentation excluded KMT2A from the list of recognized prognostic aberrations. The UKALLXII/E2993 trial included a significant population of adolescent and young adults; thus, the association of KMT2A aberrations with age simply reflects its high prevalence among adults. Indeed, its significant poor prognostic effect was clearly recognized in the adult-only cohort of UKALL14. Multiple retrospective studies identified gene deletions and CNA as prognostic in ALL. Interestingly, in the UKALL14 cohort none were dominant over cytogenetics, and the association of some of the CNA with specific cytogenetic aberrations masked its potential additive effect.

The new model suggested herein, pre-specified the patients' risk by the karyotype at presentation. The authors studied separately the effect of MRD eradication in patients with high and standard risk. However, the results should be assessed with caution. Among standard-risk patients, surprisingly, a similar relapse rate at 3 years was observed regardless of MRD status at the end of second induction (34% vs 21% for MRD-positive and negative, respectively, $p = 0.26$). Yet, no data were reported for differences in use of allogeneic stem cell transplantation, or use of "off-study" novel agents, in the MRD-positive compared to negative patients. Among the very high-risk group the relapse rate was as high as 54% even in patients who achieved molecular remission. Interestingly, in the high-risk group (i.e. KMT2A-r) the 3-year relapse rate was 69% in MRD-positive patients and only 9% among those who achieved molecular remission ($p = 0.013$).

The new risk stratification model suggested by Moorman et al. is an important step forward in providing effective tools for personalized risk-adapted therapy in B-ALL. At the same time, the model itself may well be subject to future editing since not all currently known important cytogenetic aberrations were included. Of note, Paietta et al. [5] recently published a new detailed

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cytogenetic analysis of frozen samples from the E2993 study incorporating BCL2/MYC as well as DUX4 re-arrangement that were not included in the current UKALL14 analysis. In addition, the fact that no CNA were identified by the authors as a strong prognostic marker should be further studied given the numerous studies describing the prognostic effect of PAX5 and IKZ1, CDKN2A/B and some other CNA [6–8].

In conclusion, despite the prevailing assumption that achievement of MRD supersedes other known prognostic factors, the novel cytogenetic classification proposed in this important study reiterates the significance of segregating adults with B-ALL into genetically-driven risk groups right at presentation. Such ongoing progress will hopefully foster, together with other molecular determinants, an advance in clinical decisions and contribute to improvement in patient outcomes.

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AUTHOR CONTRIBUTIONS

Authors JMR and YO wrote the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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