Leukemia (2019) 33:283–284
https://doi.org/10.1038/s41375-018-0317-4

EDITORIAL

Acute myeloid leukemia

Refining AML outcome prediction

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Received: 9 October 2018 / Accepted: 30 October 2018 / Published online: 14 December 2018

Fate laughs at probability
Edward George Earle Lytton Bulwer-Lytton,
1st Baron Lytton PC

Outcomes of people with acute myeloid leukemia (AML) are diverse even in those receiving similar therapies: some die early never achieving cytologic complete remission, others achieve cytologic complete remission but relapse whilst still others never have leukemia recurrence and appear cured. Many subject-, disease-related and therapy-related variables are reported to predict prognosis of cohorts of persons with AML. However, accuracy and precision in predicting outcomes in a person at diagnosis is imperfect: concordance (C-) statistics derived from the receiver–operator characteristic curves are only 0.7–0.8 (for binary outcomes, no predictive value is 0.5 and perfect predictive value is 1.0) [1, 2]. This inaccuracy (getting the wrong answer) and imprecision (getting different answers with repeated use) persists for subsequent outcomes even in persons achieving cytology-defined complete remission (typically defined by ≤5 percent myeloblasts in the bone marrow). Results of tests of measurable residual disease (MRD) using multi-parameter flow cytometry (MPFC), quantitative PCR (qPCR), and next-generation sequencing (NGS) platforms are claimed to improve leukemia relapse estimates [3]. But to what degree do they? Current assays are imperfect in identifying leukemia cells which, if left untreated, cause relapse, and as currently used their contribution to refining outcomes prediction is suboptimal [4].

In this issue of *LEUKEMIA*, Zeijlemaker and colleagues [5] describe MPFC quantitation of abnormal CD34-positive CD38-negative ($CD34^+CD38^-$) cells as a technique to improve accuracy and prediction of leukemia relapse in persons with AML remission after induction and consolidation therapy. Their previously described method [6] to detect these immune phenotype abnormal cells is relying on aberrant expression of ≥1 cell surface molecule on cells to differentiate abnormal from normal $CD34^+CD38^-$ hematopoietic cells. Although the relationship between phenotype and cell stem function remains controversial, measuring the concentration of cells with abnormal immune phenotypes improved outcome prediction compared with conventional approaches.

This assay was used in 594 persons with AML 18−66 years at diagnosis and 302 people achieving a cytologic complete remission after induction chemotherapy in a recent HOVON/SAKK trial [5]. Zeijlemaker and colleagues report their $CD34^+CD38^-$ assay used at diagnosis can stratify subjects into cohorts with different probabilities of achieving a cytologic complete remission and surviving. However, only the survival prediction was statistically significant in multi-variable analyses casting doubt on its predictive value as there are many competing causes of death unrelated to the probability of death from leukemia such as fatal infections or CNS bleeds in persons who would otherwise have achieved a cytologic complete remission.

Data from testing after completing induction chemotherapy suggested detection of abnormal $CD34^+CD38^-$ cells is independently associated with an increased cumulative incidence of relapse and briefer survival [5]. Importantly, data reported by Zeijlemaker and colleagues suggest $CD34^+CD38^-$ testing can increase accuracy of currently

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used MPFC and qPCR-based MRD assays in predicting outcomes in that subjects with two positive assays had worse outcomes than subjects with one positive test. Persons with no positive test had the best outcomes. This finding resembles recent reports that NGS-based MRD-testing increases predictive accuracy when combined with MPFC [7, 8].

Work toward improving MRD assays and harmonizing and standardizing them for use across institutions and laboratories is ongoing [9]. The study by Zeijlemaker and colleagues suggests such tests should include quantifying $CD34^{+}CD38^{-}$ cells with an abnormal immune phenotype. This study is a reminder of the considerable limitations of current assays of MRD and leukemia stem cells for AML. For example, the observation (in a small cohort of subjects) at a landmark timepoint the predictive accuracy of $NPM1^{mut}$ qPCR MRD-testing is improved by adding MPFC data testing for a leukemia-associated phenotype or abnormal $CD34^{+}CD38^{-}$ cells is important. Discordant results between molecular and MPFC MRD tests is reported in other studies from these authors [8]. However, if results in the current study are validated, $CD34^{+}CD38^{-}$-testing could have important implications for prognostic stratification and monitoring persons with AML. Given the increasing emphasis on NGS in all aspects of AML decision-making including MRD-testing the relationship between results of genetic tests with those from MPFC is important [10]. Finally, development of a new test to predict an increased cumulative risk of relapse and worse relapse-free survival is encouraging. The challenge is to integrate data from MRD-testing and related platforms to facilitate high-confidence predictions of the fate of someone with AML. These efforts may also result in a better understanding of leukemia biology and thereby improve therapy outcomes.

Acknowledgements This work was supported by the Intramural Research Program of the National Heart, Lung, and Blood Institute of the National Institutes of Health. CSH receives research funding from Merck Sharpe & Dohme and SELLAS Life Sciences Group AG. RPG acknowledges support from the National Institute of Health Research (NIHR) Biomedical Research Centre funding scheme. RPG is a is a part-time employee of Celgene Corp. RBW is a Leukemia & Lymphoma Society Scholar in Clinical Research.

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