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by Ann-Kathrin Eisfeld

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Unbiased decision-making for acute myeloid leukemia still needed

Ann-Kathrin Eisfeld

1Division of Hematology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH
2Clara D. Bloomfield Center for Leukemia Outcomes Research, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Correspondence: Dr. Ann-Kathrin Eisfeld, The Ohio State University Comprehensive Cancer Center, 460 West 12th Avenue, Room 500, Columbus, OH 43210-1228, USA, phone: 614-477-5667, e-mail: Ann-Kathrin.Eisfeld@osumc.edu

Outcomes of acute myeloid leukemia (AML) patients are influenced by patient-associated factors such as age1-2 and racial-ethnic identity,3 and by disease-associated factors such as select molecular aberrations.1,2 The latter consists of proliferation markers including blast counts, recurrent cytogenetic features and a growing number of AML-associated gene mutations. All together these molecular features of disease have informed our current routinely used genetic risk classifications, such as the 2017 European LeukemiaNet (ELN) risk stratification by genetics2 which directly informs treatment decisions of providers, for example, with respect to the need for an allogeneic transplant in first complete remission. With consideration of our growing knowledge of the molecular landscape and identification of driver lesions, patterns of co-existing gene mutations refined suggestions for fully genomic risk classification,4,5 and have further enhanced our assessment of the disease. As much as the establishment of these risk categories has advanced our understanding of AML and provided benefit to our patients, we are all well aware of the current limitations. The age of patients at diagnosis still carries heavy weight on survival, and both the molecular landscape and its prognostic associations differ with increasing age. As the majority of the large studies that informed the generation of prognostic stratifications are based on younger patients (<60 or 65 years), this leaves the molecular prognostic associations of older adults underrepresented. Even more knowledge- and subsequent representation gaps exist with respect to patients with
different racial-ethnic backgrounds, resulting in prognostication efforts being best suited for younger patients with European and/or European-American ancestry. With respect to disease-associated features, the increasing molecular landscape and various (sometimes contradicting) reports of prognostic significance of additional markers further complicate our clinical risk assessment.

Hence, the desire of using an unbiased approach that considers all currently known features to assess patients’ likelihood for therapy response and survival is a logic consequence.

In the study presented in this issue, Eckart et al identified predictive features for achievement of CR/CRi and 2-year overall survival using a combination of 9 machine learning algorithms for feature selection on >200 clinical and molecular parameters available for 1383 patients treated on different German cooperative study group protocols with intensive frontline chemotherapy.

They found both known and less well-described predictive features for each outcome endpoint, and validated their approach in a second, large external cohort from the AMLCG. The validation of known features, such most of our current “favorable risk” markers including inv(16), biallelic CEBPA mutations and NPM1c, and established “adverse risk” markers such as TP53, FLT3-ITD, ASXL1, RUNX1 mutations and age is reassuring and provides confidence in the identification of less established markers including variants in SF3B1, IKZF1 and/or U2AF1.

Importantly, their separate consideration of markers predictive of CR achievement and overall survival enables a more refined, and arguably clinically more useful view on predictive markers.

While there is considerable overlap between features associated with both CR and overall survival, those that do not overlap such as the positive outcome association of t(8;21) only with respect to CR achievement but not OS, may support the need of additional or different needed consolidation for those patients to translate their chemo-responsive disease also into a equal survival benefit.

The restriction to clinical parameters, cytogenetics and gene mutations may be considered a limitation to the study approach, as aberrant expression of coding and non-coding RNAs,
epigenetic changes, as well as more complex expression patterns of genomic response are known survival prognosticators. Similarly, the growing evidence of the importance of microenvironmental features and immune response are not considered in the algorithm. However, the included parameters are more widely available and thus clinically applicable with current routine methods, as validly described by the authors in their discussion. Hence, the Eckart et al. model provides a very interesting approach to help unbiased feature selection, with important distinct considerations of different outcome endpoints. The relevance is restricted to patients treated with intensive frontline chemotherapy, which again can be seen as both strength or weakness of the study: in the era of choices with respect to frontline treatment for many patients, it is highly relevant to identify especially favorable risk patients that have good chances to respond to standard induction chemotherapy. Our vulnerable older and/or unfit patients are now being treated also with several newly approved less intensive frontline treatment options such as IDH inhibitors or BCL2 inhibition/hypomethylating agents. However, for future considerations and the wish to perform similar analyses for other treatments we need to realize that extremely large, relatively uniformly treated patient cohorts are required to firmly establish response predictors to inform our choice of frontline therapy: Assembling a large enough patient cohort that enables similar machine learning approaches will be a challenge that is imperative to overcome. Quite likely, it will require collaborative efforts of many treatment centers and associated rigorous data collection and follow up to provide us with the required information and power for analyses. Furthermore, consideration of other consolidation approaches such as allogeneic transplant, maintenance therapies and measurable residual disease will be important factors — again with the challenge of finding a balance between needed cohort sizes, homogeneity of treatment, and comparable genetic and genomic backgrounds.
References


Figure Legends.

Figure 1. Machine learning approach using 9 different algorithms for optimal selection of clinical and mutational features that are predictive of achievement of complete remission upon intensive induction therapy and/or 2-year overall survival.