Unbiased decision-making for acute myeloid leukemia still needed

Ann-Kathrin Eisfeld

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

Correspondence: A-K. Eisfeld
Ann-Kathrin.Eisfeld@osumc.edu

Received: May 18, 2022.
Accepted: June 6, 2022.
Early view: June 16, 2022.

https://doi.org/10.3324/haematol.2022.281144

The outcomes of patients with acute myeloid leukemia (AML) are influenced by patient-associated factors such as age[1-2] and racial-ethnic identity,[3] and by disease-associated factors such as select molecular aberrations.[1,2] The latter factors consist 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 genetics[2] which is the basis of providers' treatment decisions, for example, with respect to the need for an allogeneic transplant in first complete remission. In consideration of our growing knowledge of the molecular landscape and identification of driver lesions, patterns of co-existing gene mutations refined suggestions for a fully genomic risk classification,[4,5] and have further enhanced our assessment of AML. 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 their current limitations. The age of patients at diagnosis still carries a heavy weight with regards to 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 larger gaps in knowledge, and subsequent representation, exist with respect to patients with different racial-ethnic backgrounds,[3] resulting in prognostication efforts being best suited for younger patients of European and/or European-American ancestry. With respect to disease-associated features, the broadening molecular landscape and various (sometimes contradictory) reports of prognostic significance of additional markers further complicate our clinical risk assessment.

The logical consequence of this is to have an unbiased approach that considers all currently known features to assess patients' likelihood of responding to therapy and surviving.

In a study presented in this issue of *Haematologica*, Eckart *et al.*[6] identified features that were predictive of achieving a complete response (with or without complete hematologic response) and 2-year overall survival using a combination of nine machine-learning algorithms for feature selection on over 200 clinical and molecular parameters available for 1,383 patients treated on different German cooperative study group (AMLCG) protocols with intensive

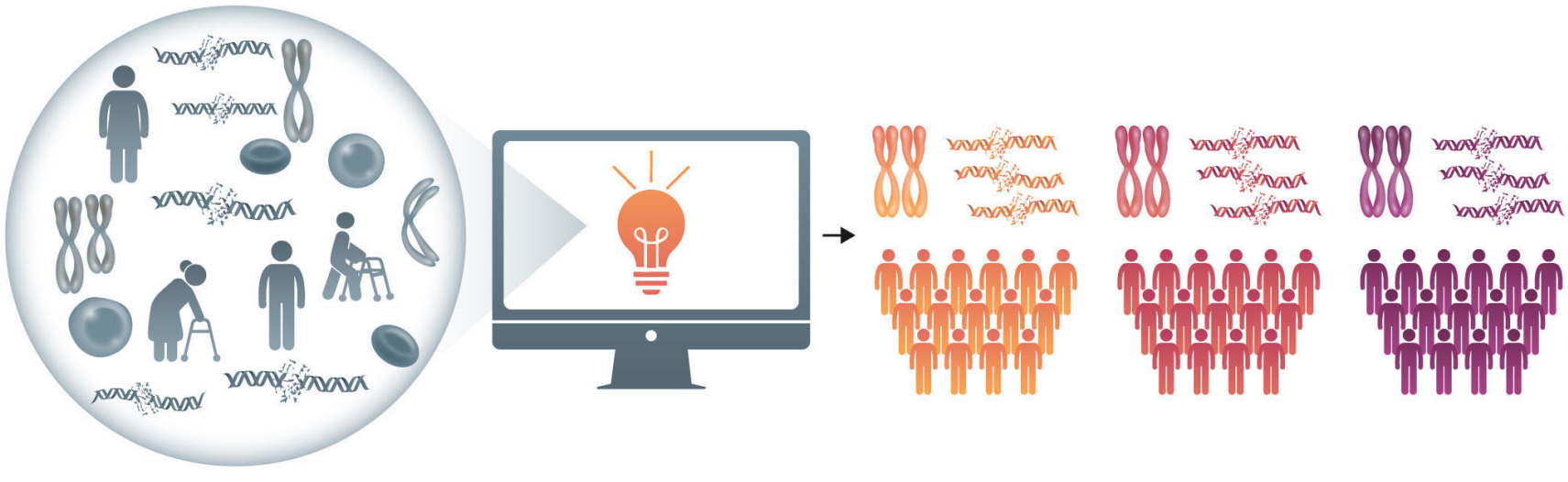

Figure 1. Machine learning in clinical prognostication. Eckardt *et al.* used a machine-learning approach including nine different algorithms for optimal selection of clinical and mutational features that are predictive of achievement of complete remission and/or 2-year overall survival upon intensive induction therapy in patients with acute myeloid leukemia.

frontline chemotherapy.[6] 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 as 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 achievement of complete response or overall survival enables a more refined, and arguably clinically more useful view of predictive markers. While there is considerable overlap between features associated with both complete response and overall survival, those that do not overlap, such as the positive outcome association of t(8;21) only with respect to achievement of complete response but not overall survival, may support the need for additional or different consolidation for those patients in order to translate their chemo-responsive disease also into an equal survival benefit.

The decision of Eckart *et al.* to restrict the algorithms to clinical parameters, cytogenetics and gene mutations may, at first sight, appear like a limitation to the study approach, as aberrant expression of coding and non-coding RNA, epigenetic changes, as well as more complex expression patterns of genomic response are known prognosticators of survival.[7] Similarly, despite the growing evidence of the importance of microenvironmental features and immune response, these are not considered in the algorithms. However, the parameters included are more widely available, making their approach clinically applicable with current routine methods, as validly described by the authors in their discussion.

Hence, the model presented by Eckart *et al.* provides a very interesting approach to help unbiased feature selection, with important, distinct considerations of different outcome endpoints.

The clinical relevance is currently restricted to patients treated with intensive frontline chemotherapy, which again can be seen as both a strength and a weakness of the study: in the era of choices of frontline treatment for many patients, it is highly relevant to identify those patients with an especially favorable risk who have good chances of responding to standard induction chemotherapy and on whom the authors provide a special focus in their analyses.

Furthermore, our vulnerable older and/or unfit patients are now being treated with several newly approved less intensive frontline treatment options such as IDH inhibitors[8,9] or BCL2 inhibition/hypomethylating agents.[10] However, for future considerations and if there is a wish to perform similar analyses for other treatments, it must be realized 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 cohort of patients to enable 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 the necessarily large cohorts, homogeneity of treatment, and comparable genetic and genomic backgrounds.

Disclosures

I do not have any conflicts of interest pertaining to this work. My spouse is employed by Karyopharm Therapeutics and is a stock holder of the company.

References

1. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med. 2015;373(12):1136-1152.
2. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.
3. Bhatnagar B, Kohlschmidt J, Mrózek K, et al. Poor survival and differential impact of genetic features of black patients with acute myeloid leukemia. Cancer Discov. 2021;11(3):626-637.
4. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic cassification and prognosis in acute myeloid leukemia. N Engl J Med. 2016;374(23):2209-2221.
5. Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. 2012;366(12):1079-1089.
6. Eckardt JN, Rölling C, Metzeler K, et al. Prediction of complete remission and survival in acute myeloid leukemia using supervised machine learning. Haematologica. 2023;108(3)690-704.
7. Ng SW, Mitchell A, Kennedy JA, et al. A 17-gene stemness score for rapid determination of risk in acute leukaemia. Nature. 2016;540(7633):433-437.
8. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med. 2018;378(25):2386-2398.
9. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood. 2017;130(6):722-731.
10. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. Blood. 2020;135(7):463-471.
11. Pollyea DA, Tallman MS, de Botton S, et al. Enasidenib, an inhibitor of mutant IDH2 proteins, induces durable remissions in older patients with newly diagnosed acute myeloid leukemia. Leukemia. 2019;33(11):2575-2584.
12. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617-629.