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MYELOID NEOPLASIA

Comment on Duchmann et al, page 2827

What can Heraclitus tell us about AML?

Arnold Ganser | Hannover Medical School

In this issue of *Blood*, Duchmann et al demonstrate the influence of comutations on the prognostic significance of isocitrate dehydrogenase (*IDH*) mutations in adult patients with newly diagnosed acute myeloid leukemia (AML) treated with intensive chemotherapy (IC) and followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT) in eligible patients.[1]

In *IDH1*- and *IDH2R140*-mutated AML treated with IC, the cooccurrence of an *NPM1* mutation is the most important prognostic factor with favorable influence on overall survival (OS). *IDH*-mutated AML with additional poor prognostic features, according to the scoring system of the European LeukemiaNET (ELN 2010), benefits from allo-HSCT in first complete remission (CR1).

AML is now regarded as a group of hematopoietic neoplasms that are characterized by a sequence of genetic alterations which, in their complex hierarchical architecture, influence AML pathogenesis and are also responsible for heterogeneity in clinical presentation and outcome.[2] Recent advances have resulted in the characterization of distinct molecular groups that predict the individual likelihood of a patient to respond to treatment, risk of disease progression, relapse, and death.[3] Some of these genetic subclasses have already been included in the 2016 World Health Organization revised classification of AML subgroups, namely mutations of *NPM1*, *CEBPα*, and *RUNX1*.[4] Mutations of *IDH1* and *IDH2* are not among these subclass-defining mutations.

Point mutations in *IDH1* and *IDH2* genes are rather common in adult AML, present in 7% to 14% and 8% to 19% of patients, respectively.[2] Mutated enzymes produce excess amounts of an oncometabolite, D-2-hydroxglutarate with transforming activity. Oral inhibitors of mutant IDH1 and IDH2 enzymes have been developed and recently approved by the US Food and Drug Administration (FDA) as single agents for the treatment of relapsed/refractory AML with mutated *IDH1/2* and for newly diagnosed AML with mutated *IDH1*. Randomized trials with a combination of IDH inhibitors and IC in newly diagnosed AML are ongoing. Therefore, an improved definition of the genetic risk classification of each *IDH* mutation subtype is particularly relevant.

Although they share a common oncogenic mechanism, the most common *IDH* mutation subtypes (*IDH1R132*, *IDH2R140*, *IDH2R172*) have different landscapes of cooccurring mutations that impact prognosis and response to treatment.[3,5,6] Thus far, risk stratification of AML patients carrying *IDH* mutations and undergoing intensive induction chemotherapy has been difficult, producing conflicting results.[7] Ergo, *IDH* mutations do not play a role in the ELN 2010 and ELN 2017 scoring systems.[4,8] This retrospective analysis of 3 prospective clinical trials of the Acute Leukemia French Association (ALFA) looked at the prognostic impact of clinical and genetic covariates and the outcome of allo-HSCT in a large cohort of 319 newly diagnosed *IDH*-mutated AML patients. Apart from conventional cytogenetics, the molecular genetic analysis focused on the 37 genes overlapping in the 3 studies. The 2 major conclusions are that the presence of an *NPM1* mutation and a normal karyotype defined a subgroup with better OS, whereas in patients with nonfavorable ELN 2010 scores, allogeneic stem cell transplantation (allo-HSCT) improved both OS and disease-free survival.

What do the data tell us and what are the limitations? The study adds a considerable amount of data on the impact of IDH subtypes and comutations and serves as a baseline for the clinical trials with IDH inhibitors. First, the IDH subtypes present in different biological ways and have different outcome after IC and therefore should be looked at separately in future clinical trials. The presence of a concurrent *NPM1* mutation is the main prognostic factor for a good response to IC in *IDH1*- and *IDH2R140*-mutated AML. This could serve as an argument to stratify IDH-mutated AML in the ongoing or planned clinical trials with IC and IDH inhibitors according to the *NPM1* mutation status. However, because this behavior is only seen in patients with wild-type *DNMT3A*, as has been previously reported for the *NPM1/DNMT3A/FLT3*–internal tandem duplication triple mutation,[3] the stratification rules might need to become more complex the more we learn about these interactions. In addition, the implementation of IDH inhibitors in our treatment strategies might influence the prognostic impact of certain mutations. Other new drugs like venetoclax also have surprisingly good activity against *IDH*-mutated leukemic blast cells in vitro.

The present study shows that patients with nonfavorable ELN 2010 *IDH*-mutated AML did benefit from allo-HSCT in CR1. Thus, the presence of *IDH* mutations did not change the risk stratification and should not alter the current treatment recommendations. Again, the situation will have to be reevaluated after the integration of the IDH inhibitors, or drugs like venetoclax,

in the IC protocols both during induction and maintenance.

Is there a way out of this complex conundrum? The simple answer is no. The complexity of clinical care of AML will increase with our increasing knowledge. In the future, we will have to integrate clinical, genetic, and metabolic factors with the outcome obtained with each treatment protocol. This could include outcomes like residual disease, OS, relapse risk, and need/benefit of allo-HSCT, into models that will lead to a more personalized approach to patient care using knowledge banks.[9] This will require continuous collaborative efforts, and the article by Duchmann et al represents some of the first steps. We have to be aware as clinicians that many uncertainties remain. With these mutations, we must also be aware that these *IDH* mutations through the oncometabolite may impair organ function outside of the hematopoietic system.[10] Expanding registries run by the Research Collaborative of the American Society of Hematology, or the Innovative Medicines Initiative HARMONY project in Europe, will certainly pave the way for future developments.

As Heraclitus already said 2500 years ago: "everything is in flux" (πάντα ῥεῖ).

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