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Silver bullets for the golden age: treating *IDH*-mutated acute myeloid leukemia in older patients

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The recent decade has been an exciting one for those involved in caring for patients with acute myeloid leukemia (AML). Characterizing the genetic, epigenetic and metabolic pathways underlying the initiation and progression of AML has led to the development and approval of multiple targeted therapies that have impacted clinical practice and patient outcomes. These advances have been especially meaningful for patients over 60 years of age, a population characterized by adverse genetics, increased comorbidity burden, and poor prognosis[1].

In the current issue, Hoff et al.[2] report on the prevalence and clinical impact of isocitrate dehydrogenase (*IDH)1* and *IDH2* mutations in a large cohort of patients with AML enrolled to the 'Beat AML' trial, a multicenter umbrella trial that allocates patients over age 60 years to various investigational targeted interventions based on their dominant somatic clone (NCT03013998). The investigators report that 28% of over one-thousand patients analyzed had *IDH1*/*2* mutations (*IDH1* 9.7%, *IDH2* 18.9%). They further demonstrate that while *IDH* mutational status did not affect outcome in patients treated with intensive induction chemotherapy (IC), *IDH* mutations predicted better outcomes in patients treated with lower intensity therapy, specifically with hypomethylating (HMA)-based approaches, This effect was mainly driven by *IDH*2 mutations and noted even when *IDH* was co-mutated with mutations carrying adverse prognosis such as *TP53,* complex karyotype*,* and myelodysplasia-related, secondary-type mutations (STM).

Mutations in *IDH1* and *IDH2* (*located* in the cytoplasm and in the mitochondria, respectively) occur in approximately 20% of patients with newly diagnosed AML[3]. These genes encode nicotinamide adenine dinucleotide phosphate $(NADP)^{+}$-dependent enzymes that mediate the reversible oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) in the tricarboxylic acid (TCA) cycle, while generating NADPH, an essential cofactor that maintains cellular redox homeostasis and supports energy production. Somatic gain-of-function mutations, most frequently *IDH1-R132* and *IDH2-R140*, or *R172,* are associated with neomorphic enzymatic activity that reduces α-KG to the oncometabolite 2-hydroxyglutarate (2-HG). Accumulation of 2-HG competitively inhibits α-KG–dependent dioxygenases, including TET2 and histone demethylases, leading to widespread DNA and histone hypermethylation, impaired differentiation, and leukemic transformation. Elevated 2-HG also interferes with hypoxia-inducible factor (HIF) prolyl hydroxylases, stabilizing HIF-1α and creating pseudohypoxic conditions that

further drive leukemogenesis. *IDH1* mutations are associated with enhanced oxidative TCA cycle activity and reduced reductive glutamine metabolism, resulting in increased dependence of leukemic cells on mitochondrial oxidative phosphorylation[3].

IDH-mutated leukemias exhibit metabolic vulnerabilities amenable to targeted interventions (Fig. 1). *IDH*-mutated myeloid neoplasms have previously been shown to be *BCL2*-dependent[4], and previous clinical observations (excluding the current analysis by Hoff et al.[2]) suggest that venetoclax-containing therapies are effective in patients harboring *IDH mutations[5].*

Inhibition of *IDH1* and *IDH2* with the small molecule inhibitors (*IDHi*), ivosidenib and enasidenib, and the more recently approved *IDH1i* olutasidenib, demonstrate activity in relapsed/refractory (R/R) *IDH*-mutated AML[3]. In the upfront setting, the combination of azacitidine with ivosidenib was associated with higher remission rates and better survival as compared to azacitidine therapy alone (hazard ratio for death, 0.44; 95% CI, 0.27 to 0.73; P = 0.001)[6] and is currently FDA approved for this indication. *IDH2* inhibition in the upfront setting is not yet approved although early phase trials demonstrate encouraging efficacy signals[7].

In the most recent European LeukemiaNet (ELN) framework for genetic risk stratification of patients receiving less-intensive therapies, *IDH*-mutated cases are categorized as favorable-risk (“higher-benefit group”). This classification underscores the efficacy of lower-intensity, targeted approaches in this molecular subset and illustrates a key principle that genetic risk attribution in AML is dependent not only on the objective somatic landscape, but also on the treatment approach chosen[8].

Co-mutation patterns affect the prognostic and predictive impact of single somatic mutations in AML. Interestingly, Hoff et al.[2] show that *IDH* mutations retained their favorable impact for HMA-based treated patients even in the context of high-risk co-mutations. For example, patients with *TP53*-mutations and STMs that also harbored *IDH*-mutations, did better than their *IDH* wild-type counterparts, especially when treated with *IDHi.*

Several challenges and unanswered questions remain. For *IDH1*-mutated patients, the physician faces an 'embarrassment of the riches' as both HMA-venetoclax and HMA-ivosidenib represent viable, standard of care options. A recent retrospective analysis demonstrated that the latter approach may be associated with higher remission rates,

lower rates of febrile neutropenia, and with higher rates of transition to allogeneic transplantation as compared to HMA-venetoclax[9], although this has not been validated in a prospective, controlled setting.

Despite the significant increase in response and survival with the introduction of HMA-based targeted therapies, disease resistance remains a major cause of treatment failure and death with these approaches. Augmenting therapy with triplet approaches (e.g. HMA plus venetoclax plus *IDHi*) is associated with high response rates and encouraging survival[10]. The efficacy and toxicity of these approaches should be balanced and further validated in randomized controlled trials comparing them to established HMA -based regimens before being recognized as the new standard of care for *IDH*-mutated AML.

Finally, the role of targeted interventions for patients with *IDH* mutations treated with IC is still unclear. Preliminary data suggest potential efficacy of venetoclax combined with IC for this subgroup[11]. Incorporation of *IDHi* to IC regimens for this patient population was shown to be well-tolorated[12],and is currently tested in the highly anticipated phase 3 HOVON150 clinical trial that incorporates *IDHi* to all treatment stages, including a post-remission maintenance phase (HOVON150, NCT03839771).

In summary, Hoff et al.[2] add valuable insights to the evolving treatment paradigm of patients with *IDH*-mutated AML. They confirm the high prevalence of these mutations in older patients and the benefit of HMA-based therapies in this population subset, including in the context of co-mutations with high-risk genetics. Incorporation of triplet lower-intensity combinations may prove to be the next step in further improving outcomes for *IDH*-mutated patients.

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Figure 1: Treating *IDH*-mutated AML. Current approach and prospects.

AML: Acute myeloid leukemia, Aza: azacitidine, HMA: hypomethylating agents, Ena: enasidenib, IC: intensive chemotherapy, *IDH*: isocitrate dehydrogenase, Ivo: ivosidenib, LDAC: low-dose cytarabine, SOC: standard-of-care, Ven: venetoclax