socitrate dehydrogenase (IDH) driver mutations are detected in 20% of patients with acute myeloid leukemia (AML). Abnormal function of IDH1 and IDH2 genes involves metabolic and epigenetic cellular changes. IDH1 and IDH2 mutations generate an accumulation of 2-hydroxyglutarate (2-HG) leading to DNA hypermethylation, aberrant gene expression, and cell proliferation with impaired cellular differentiation (Montalban-Bravo & DiNardo, 2018). Both IDH1 and IDH2 mutations induce BCL-2 dependence through inhibition of cytochrome c oxidase leading to a lower apoptotic threshold of BCL inhibition (Chan et al., 2015).

IDH mutations often (85%) occur in de novo AML, diploid, or trisomy 8 and are more prevalent with increasing age. The frequency of mutations increases from lower to higher-risk disease, suggesting a role in disease progression (Molenaar et al., 2015). Roughly 25% of patients with a myeloproliferative neoplasm (MPN) will acquire an IDH mutation at time of progression to AML.

The primary therapeutic approach is intensive cytotoxic chemotherapy and consolidative chemotherapy. Elderly patients and those with relapsed/refractory (R/R) AML are often unable to tolerate intensive chemotherapy and do not have the option to proceed with allogeneic stem cell transplantation.

U.S. Food and Drug Administration approvals of enasidenib (Idhifa; Agios Pharmaceuticals, formerly AG-221) and ivosidenib (Tibsovo, formerly AG-120) have allowed for a safe and well-tolerated treatment option that has also been shown to induce hematologic responses in this patient population.

**ENASIDENIB**

Enasidenib is an oral selective inhibitor of mutant IDH2 enzymes. A phase I/II study evaluated the response, tolerability, and safety of AG-221 in R/R AML. The overall response rate (ORR) was 40.3% with a median overall survival (OS) of 9.3 months, and a 1-year OS of 39%. In newly diagnosed AML, the median OS was reported as 11.3 months. Even with monotherapy, patients were found to have improved responses and survival when enasidenib was used in earlier stages of treatment.
Enasidenib, when used to treat unfit patients with newly diagnosed mutant IDH2 AML, showed 2-HG reductions of 97.8% in the enasidenib plus azacitidine arm compared with 54.3% in the azacitidine alone arm. This combination therapy improved the ORR from 42% to 71%, complete remission (CR) from 12% to 53%, and median event-free survival from 10.4 months to 17.4 months. Enasidenib monotherapy, when given in combination with 5-azacitidine, improves both response and survival.

**Key Points**
Notable mechanisms of relapse and patterns of clonal selection (associated with increased 2-HG) when patients begin to lose response to an IDH inhibitor include:
- Presence of second site mutations of IDH1 and IDH2 leading to restoration of 2-HG, indicating that 2-HG reduction alone is not sufficient (Choe et al., 2020).
- Primary resistance with co-occurring mutations at baseline. One such is receptor tyrosine kinase (RTK) mutations, which are more associated with mutant IDH1 R/R AML.
- Secondary resistance to enasidenib after clinical response was associated with emergence of AML-related mutations (RUNX1, GATA2, FLT3). Reconstitution of a differentiation block.
- Isoform switching: acquired mutant IDH2 in IDH1-mutant clone with elevation of 2-HG at relapse.

Enasidenib-induced indirect hyperbilirubinemia occurred in 35% of patients, possibly due to off-target inhibition of the UGT1A1 enzyme responsible for bilirubin metabolism (Stein et al., 2017). Non–dose-dependent, noninfectious leukocytosis occurred in 17% of patients within the first 2 cycles.

**IVOSIDENIB**
Ivosidenib is an oral small-molecule inhibitor of mutant IDH1. A phase I study evaluating the safety and tolerance of AG-120 in R/R AML yielded an ORR of 39.1% with a median OS of 8.8 months and 18-month OS of 50.1%. Ivosidenib induced myeloid differentiation without a period of bone marrow aplasia (DiNardo et al., 2018).

Common adverse effects included diarrhea (30.7%), leukocytosis (29.6%), febrile neutropenia (28.5%), nausea (27.9%), dyspnea (24.6%), QT prolongation (24.6%), peripheral edema (21.8%), and cough (20.7%; DiNardo et al., 2018).

The AGILE double-blind study of azacitidine plus ivosidenib for newly diagnosed AML is ongoing and currently has a CR rate of 36.7% vs. 17.9% in the azacitidine-only arm.

**VENETOCLAX**
IDH2 mutations induce BCL-2 dependence by mediating inhibition of cytochrome c oxidase leading to a lower threshold triggering apoptosis with BCL-2 inhibition. Preclinical data confirms synergistic activity of IDH inhibitors plus venetoclax (Venclexta).

**COMBINATION THERAPY AND FUTURE DIRECTIONS**
Given the effectiveness of IDH1/2 inhibitors in the relapsed/refractory AML setting, a phase I study was created to evaluate the safety and efficacy of enasidenib and ivosidenib combined with intensive chemotherapy in patients with newly diagnosed AML with mutated IDH1/2 (Stein et al., 2021).

A phase Iib trial of ivosidenib plus venetoclax plus azacitidine is currently enrolling patients.Although early, out of six patients initially progressing on hypomethylating agent–based therapy +/- venetoclax who relapsed with an IDH1 mutation, five were able to achieve another remission. This demonstrates the synergy of IDH inhibitors and venetoclax. Newly emerging data reveal continuous response.

The Advanced Practitioner Perspective
Emerging data from clinical trials evaluating novel agents require advanced practitioners to stay current to improve the quality of care of patients with AML. Elderly and R/R AML patients remain a population with minimal options who can benefit from low-intensity combination chemotherapy. Despite the availability of oral therapy, IDH inhibitors (whether given as monotherapy or in combination) still have the potential for adverse effects. It is imperative that advanced practitioners understand the mechanism of action and educate patients on both expectations and toxicities of therapy.

Disclosure
Ms. Geppner has served as a consultant and advisor for AbbVie.
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