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Isocitrate dehydrogenase mutations in myeloid malignancies

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INTRODUCTION
Acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) are heterogeneous myeloid disorders with multifactorial pathogenic mechanisms and a broad range of prognoses. AML is characterized by clonal proliferation of poorly differentiated cells of the myeloid lineage. MDS reflects the presence of dysplasia and ineffective hematopoiesis commonly leading to bone marrow failure and insufficiency, with a resultant decrease in peripheral blood counts. The pathogeneses of both involve recurrent genomic alterations, including somatic gene mutations and/or chromosomal abnormalities, that can define biologically distinct clinical subtypes. Comprehensive genomic profiling at the time of diagnosis can inform disease classification, risk stratification and prognosis and ultimately allow for more selective therapeutic interventions.

Alterations to cellular metabolism, as well as somatic mutations of genes essential to epigenetic regulation, are implicated in the pathogenesis of several human malignancies. Isocitrate dehydrogenases (IDHs) are homodimeric enzymes involved in diverse cellular processes, including adaptation to hypoxia, histone demethylation and DNA modification. The IDH2 protein is a critical component of the tricarboxylic acid (also called the ‘citric acid’ or Krebs) cycle, and both IDH2 and IDH1 proteins catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG). Mutant IDH enzymes have neomorphic activity and catalyze reduction of α-KG to the (R) enantiomer of 2-hydroxyglutarate, which is associated with DNA and histone hypomethylation, altered gene expression and blocked differentiation of hematopoietic progenitor cells. The prognostic significance of mutant IDH (mIDH) is controversial but appears to be influenced by co-mutational status and the specific location of the mutation (IDH1-R132, IDH2-R140, IDH2-R172). Treatments specifically or indirectly targeted to mIDH are currently under clinical investigation; these therapies have been generally well tolerated and, when used as single agents, have shown promise for inducing responses in some mIDH patients when used as first-line treatment or in relapsed or refractory AML or MDS. Use of mIDH inhibitors in combination with drugs with non-overlapping mechanisms of action is especially promising, as such regimens may address the clonal heterogeneity and the multifactorial pathogenic processes involved in mIDH myeloid malignancies. Advances in mutational analysis have made testing more rapid and convenient, and less expensive; such testing should become part of routine diagnostic workup and repeated at relapse to identify patients who may benefit from treatments that target mIDH.

IDH MUTATIONS IN AML AND MDS
Mutant IDH enzymes have neomorphic activity, catalyzing NADPH-dependent reduction of α-KG to an oncometabolite, the α-KG analog 2-hydroxyglutarate (2-HG). Mutant IDH enzymes also catalyze the e-NADP(+) to NADPH reaction, generating NADPH (Figure 1). Diverse dioxygenases depend on sufficient levels of α-KG for multiple cellular processes, as well as for epigenetic regulation. IDH1 enzymes are localized to the cytoplasm and peroxisomes and IDH2 to the mitochondria. Somatic mutations in IDH1 (IDH1-R132 and IDH2-R172) genes have been described in both solid and hematological malignancies; IDH1-R132 is more common in solid tumors and IDH2-R172 is more common in hematological tumors. IDH1/2 mutations are heterozygous, retaining one wild-type (wt) allele, suggestive of an oncogenic gain of function. IDH1/R132C and IDH2/R172K mutations are encoded by the IDH1 gene located at chromosome 2q33 and the IDH2 gene residing at chromosome 15q26. An IDH3A isoform is also located in the mitochondria, but no oncogenic mutations in the IDH3 gene have been reported to date. Recurrent IDH1/2 mutations are missense variants leading to a single amino-acid substitution of arginine residues at codon 132 in exon 4 of the IDH1 gene and codons 140 or 172 in exon 4 of the IDH2 gene. Additionally, a germline-synonymous single-nucleotide polymorphism (rs11554137) located in exon 105 in exon 4 of the IDH1 gene has been reported to have prognostic relevance in AML.

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(R)-enantiomer of 2-hydroxyglutarate ((R)-2-HG, also called 2-oxoglutarate) in vitro and in vivo. Increased levels of the (S) enantiomer of 2-HG have not been reported in AML or MDS. In an AML xenotransplantation model established from a patient with wtIDH1 and mutant nucleophosmin 1 (NPM1), (R)-2-HG but not (S)-2-HG acted as an oncometabolite and daily administration of (R)-2-HG was associated with significantly reduced platelet counts and shorter survival than (S)-2-HG-treated mice. High concentrations of (R)-2-HG lead to enhanced proliferation and arrested differentiation of hematopoietic progenitors. Serum from patients with mIDH AML contains levels of (R)-2-HG that are more than 100-fold higher than expected under normal physiological conditions.

(R)-2-HG is structurally similar to α-KG and has been shown to competitively inhibit α-KG-dependent enzymes, including members of the ten-eleven-translocation (TET) family of 5-methylcytosine hydroxylases and of the jumonji-domain-containing group of histone lysine demethylases. Similarly, histone demethylases regulate chromatin status, enabling activation or inhibition of gene transcription. Inhibition of these epigenetic regulators by (R)-2-HG produces a hypermethylation signature, altering gene expression and leading to differentiation arrest of hematopoietic progenitors. Figueroa et al. evaluated the mutational and epigenetic profiles of 385 AML patients aged <60 years; patients with mIDH1/2 AML exhibited a global hypermethylation phenotype associated with significant suppression of gene expression compared with patients with wtIDH1/2 AML. Although both mIDH1 and mIDH2 enzymes encode (R)-2-HG, they have different enzymatic activities. Cytoplasmic mIDH1 generates less (R)-2-HG than mitochondrial mIDH2 enzymes. This may be due to differences in amounts of α-KG substrate, which is found in greater abundance in the mitochondria than in the cytoplasm. (R)-2-HG production is enhanced in the presence of mIDH1/wtIDH1 heterodimers, suggesting that the retained wtIDH1 enzyme produces some of the α-KG that is reduced to (R)-2-HG. In contrast, mIDH2 homodimers can produce abundant (R)-2-HG. Mutated IDH2-R172 protein leads to greater accumulation of (R)-2-HG than mIDH2-R140 protein in vitro.

**EPIDEMIOLOGY**

Taken together, mIDH1/2 are among the most common mutations in AML (~20% of patients combined, Table 1). IDH mutations increase in frequency with increasing age. mIDH are less frequent in MDS (~5%) and myeloproliferative neoplasms, although the frequency increases to ~20% of patients with myeloproliferative neoplasms at leukemic transformation. Mutant genes involved in epigenetic regulation, including mIDH, may exist in preleukemic stem cells, which retain the ability to differentiate into multiple lineages, can survive chemotherapy and proliferate during remission, eventually leading to relapse.

**Table 1. Frequencies of common recurrent gene mutations in adults with AML or MDS**

| Mutated gene | Frequency in AML1 | Frequency in MDS1,2,3,4,5 |
|--------------|-------------------|--------------------------|
| NPM1         | 25–35%            | 2%                       |
| DNMT3A       | 18–22%            | 8%                       |
| FLT3-ITD     | ~20%              | 0–2%                     |
| TET2         | 7–25%             | 11–26%                   |
| IDH2         | 8–19%             | ~5%                      |
| AXL5         | 5–17%             | 11–15%                   |
| RUNX1        | 5–15%             | 4–14%                    |
| NRAS         | ~15%              | 3–6%                     |
| IDH1         | 7–14%             | 3%                       |

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

![Figure 1. IDH mutations in cancer. Mutant IDH1 and IDH2 enzymes result in an increase of the oncometabolite, (R)-2-HG. (R)-2-HG induces a block of cell differentiation by inhibiting the activity of chromatin-modifying histone and DNA demethylases. Inhibition of these epigenetic regulators leads to a ‘hypermethylation signature’ that alters gene expression such that cells lose the ability to progress from immature progenitors to a fully differentiated state.](Image)
AML. Co-occurrence of miDH and Fms-related tyrosine kinase 3 (FLT3) mutations are less common,\textsuperscript{44} Marcucci et al.\textsuperscript{19} reported clinical outcomes for 358 patients with de novo CN-AML; results showed that patients with miDH1 were less likely to have FLT3-internal tandem duplication (FLT3-ITD). Interestingly, compared with other types of miDH, miDH2-R172 is less likely to be accompanied by additional frequently recurring mutations in AML (for example, FLT3-ITD, CCAAT/enhancer-binding-protein-alpha (CEBPA) or NPM1).\textsuperscript{10,40,43}

**PROGNOSIS**

The prognostic impact of miDH1/2 in AML remains controversial. Several studies have suggested an association with adverse outcomes,\textsuperscript{10,37,38,48,49} whereas others have failed to identify any clear influence on clinical response or survival\textsuperscript{11,35,30,51} and still others report improved survival (Table 2).\textsuperscript{50,44} A meta-analysis that included 8121 patients with AML showed that those with miDH1 had inferior OS compared with patients without the mutation, and patients with miDH1 CN-AML had a lower rate of complete remission (CR) with cytotoxic induction chemotherapy.\textsuperscript{46} Indeed, a preponderance of studies suggest miDH1 AML confers an adverse prognosis or has no prognostic value (Table 2). One study found no influence of miDH1-R132 on OS, but the IDH1 single-nucleotide polymorphism rs11554137 variant was associated with an adverse prognosis.\textsuperscript{11} Analyses of the prognostic impact of IDH2 mutations also show inconsistent results; for example, in one study of patients with CN-AML, miDH2 had no effect on OS or CR rate compared with wild-type IDH2,\textsuperscript{52} but in another study, miDH2 was associated with lower rates of CR, higher relapse rates and shorter OS.\textsuperscript{43}

Differences in prognostic findings may reflect variations in study methodologies. Some studies evaluate miDH by point mutation and others combine miDH1/2 for analysis.\textsuperscript{49,51,53} Specifically, with regard to miDH2, R172 and R140 mutations are frequently analyzed together, although data suggest that these mutations have different effects on prognosis (Figure 2).\textsuperscript{1,10,44,54} Recently, Papaemmanuil et al.\textsuperscript{36} proposed new genomic classifications for AML, including (provisionally) 'AML with miDH2-R172' as a distinct class, and recommended that IDH2 testing be added to prognostic guidelines. In their study of 1540 AML patients, AML with miDH2-R172 was not accompanied by other class-defining lesions (for example, FLT3, NPM1) and was associated with gene-expression and DNA-methylation profiles seen with more severe abnormalites in metabolic activity, compared with other IDH mutations. Nevertheless, unlike earlier reports,\textsuperscript{10,44,54,55} investigators found miDH2-R172 to have a relatively favorable effect on AML prognosis.\textsuperscript{56} Mutational context may influence AML prognosis, but again, this is unclear. For example, there is conflicting evidence regarding prognosis of patients with miDH1/2 in the presence of NPM1 mutations and FLT3-ITD\textsuperscript{1}; with some data suggesting a better prognosis and others reporting worsened outcomes or no influence of this mutational profile.\textsuperscript{35,38,44,49,51,55,57}

Patel et al.\textsuperscript{44} conducted a large study (N = 398) to determine the prognostic relevance of frequent somatic mutations in younger patients (< 60 years) with AML, which showed a favorable effect of co-occurring mutated NPM1 and miDH1 or miDH2. These data were further supported using a proposed integrated prognostic model that combined cytogenetic risk and mutational status using retrospective data from younger patients with newly diagnosed de novo AML.\textsuperscript{58} In this model (which has not yet been validated clinically), the presence of co-occurring IDH1/2 and NPM1 mutations in patients with intermediate-risk cytogenetics per Medical Research Council criteria was associated with median OS comparable to that of patients with Medical Research Council-defined favorable cytogenetic risk.\textsuperscript{59} In contrast, Paschka et al.\textsuperscript{38} reported that the subset of patients with CN-AML with a miDH1/ NPM1/’ FLT3-ITD’ genotype in their study had significantly poorer

![Table 2](image-url)
OS than patients with mIDH CN-AML who did not have that genotype. Generally, mIDH2-R140 is much more likely to be accompanied by mutated NPM1 or other frequently recurring mutation in AML or MDS than mIDH2-R172.10,55,56

IDH1/2 mutations appear to have a more consistently negative prognostic impact in MDS and myeloproliferative neoplasms than in AML.59,60 A study of 193 patients with MDS showed that mIDH1 was associated with shorter OS compared with patients with wtIDH and greater likelihood of leukemic transformation (67% vs 28%, respectively).59 These findings were confirmed by results of a meta-analysis of seven studies that included a total of 1782 MDS patients.60 The relative prognostic impact of type of IDH mutation in MDS is uncertain; Bejar et al.61 reported that, based on survival data for 3200 patients with MDS, mIDH2 was associated with significantly shorter OS, whereas mIDH1 had only a marginal effect on OS. Other studies suggest mIDH1 confers worse prognosis than mIDH2 in MDS.59,62 The prognostic influence of mIDH type may depend on patients’ overall prognostic risk status.46,61 Lin et al.46 reported that mIDH2 was a poor prognostic factor in patients with lower-risk MDS, based on International Prognostic Scoring System, revised International Prognostic Scoring System, French–American–British classification or World Health Organization classification, but not in the higher-risk groups.

Serum (R)-2-HG concentration may also serve as a prognostic indicator.63 Of 234 patients with CN-AML, a subgroup of patients who met an (R)-2-HG threshold at diagnosis that the investigators established as ‘high’ (>2.01 μg/ml, log2) were less likely to attain CR and had significantly poorer OS than patients in the ‘normal’ (R)-2-HG group (Figure 3). Posttreatment (R)-2-HG levels may also have prognostic implications. In a study of 223 younger patients with de novo AML treated with standard induction chemotherapy including 62 patients with mIDH, patients in CR who had higher serum levels of (R)-2-HG had poorer OS than patients in CR with lower levels of (R)-2-HG.64 This study showed that (R)-2-HG levels were not significantly different among the different mutation types (mIDH1, mIDH2-R140 or mIDH2-R172); however, there was a trend for poorer OS for the small number of patients (n = 9) with mIDH2-R172.64 A different study also found a significant quantitative relationship between (R)-2-HG level and posttreatment clinical outcomes: serum (R)-2-HG concentrations of ≥2 μmol/l were associated with poorer OS and disease-free survival.65 In the latter study, IDH2-R172 mutations were associated with significantly higher levels of (R)-2-HG compared with the other IDH mutation types.

Further investigation is needed to more clearly elucidate the relationship between (R)-2-HG levels and clinical outcomes.

**DETECTION**

Because IDH mutations occur in approximately one in five patients with AML, and even more frequently in patients with CN-AML, mutational testing should be part of routine molecular assessment at diagnosis to identify patients who may in time benefit from targeted treatments currently under clinical study.37 Identification of these mutations at diagnosis may also be pivotal for better risk stratification of MDS patients.50

![Figure 2](image2.png)

**Figure 2.** Location of IDH2 mutation may influence prognosis in AML. OS in 148 adult patients with IDH2-mutation-positive AML treated in two Medical Research Council (MRC) trials (Republished with permission of the American Society of Hematology; from Green et al.55)

![Figure 3](image3.png)

**Figure 3.** (R)-2-HG level may serve as a biomarker of prognosis and treatment effects. OS in patients with cytogenetically normal AML with high or normal levels of (R)-2-HG (Adapted from Wang et al.63).
Testing for mIDH is straightforward, given that nearly all IDH mutations are located on exon 4, and affect IDH1 at a single residue, Arg132, or IDH2 at two residues, Arg140 and Arg172. Several methods, including PCR, Sanger or next-generation sequencing, are commonly used for mIDH detection.

High-resolution melting (HRM) analysis is a rapid, sensitive and cost-effective method of genotyping and mutational analysis. HRM detects sequence differences that change the shape of the melting curve of DNA. A comparison between Sanger sequencing and HRM analysis showed 99–100% concordance of mutation detection but much greater sensitivity with the HRM technique, which detected mutations in samples diluted to only 10% of the mutated DNA. As a heterozygous mutation, the highest detectable IDH variant allele fraction (VAF) is 50% and a recent report on 664 adult AML patients by Metzeler et al. indicated that, for patients with miDH2, VAF, on average, approached 50%. At this time, there is no established or standard VAF threshold to identify miDH as a leukemogenic driver at diagnosis. A too-low VAF positivity threshold (for example, < 2%) may have ambiguous clinical relevance and could be a signal of clonal hematopoiesis of indeterminate potential (CHIP). Prevalence of CHIP, a hematological malignancy-associated somatic mutation in the absence of other diagnostic features of MDS or AML, increases with age. Despite relatively high prevalence in older patients, the presence of leukemia-associated mutations is followed by a hematological malignancy in only a minority of cases.

Many hospitals, particularly those affiliated with academic medical centers, perform mutational analyses with next-generation sequencing using MDS/AML gene panels. Private laboratories also perform these multiplex panels for diagnostic and prognostic purposes. A list of laboratories that conduct mutational analyses is available on the National Center for Biotechnology Information website (http://www.ncbi.nlm.nih.gov/gtr/).

IDH mutations detected at diagnosis tend to be stable during disease progression. Assessmental of 151 patients with MDS demonstrated that all miDH patients retained the mutation during disease evolution, while none of the wtIDH patients acquired an IDH mutation during follow-up. However, variations in detection limits or expansion of the mutant clone over time can account for the presence of seemingly new mutations at relapse not previously detected at diagnosis. In one study, 5.7% of MDS patients were identified as having an IDH mutation at diagnosis, whereas 11.3% of patients had an IDH mutation at the time of leukemic transformation, demonstrating the value of comprehensive molecular profiling at disease progression.

IDH1/2 mutations may also be suitable molecular markers of minimal residual disease with standard intensive chemotherapy approaches. Paired diagnosis and relapse samples demonstrated that miDH1/2 cells can survive induction chemotherapy and contribute to relapse. A study of patients with NPM1-mutant AML with concurrent IDH1/2 (n = 17) or DNMT3A (n = 15) mutations revealed that IDH1/2 mutations were reliable markers of minimal residual disease for 16 of the 17 patients: 7 of the 8 patients with detectable miDH1/2 in CR eventually relapsed, whereas all 9 patients with undetectable miDH1/2 remained in CR for the duration of the study. This is distinct from treatment with targeted small-molecule miDH inhibitors, where emerging data demonstrate CR in the setting of alleviation of maturation arrest—without chemo-ablation or destruction of the mutant clone.

Mutational persistence during remission and the potential that a low VAF is indicative of CHIP in older patients (a VAF threshold of ≥ 2% in peripheral blood has been proposed as a diagnostic criterion of CHIP) complicate the use of miDH as a marker of minimal residual disease.

Supranormal levels of (R)-2-HG may serve as a noninvasive biomarker of IDH mutations. Plasma can be measured by liquid or gas chromatography coupled with mass spectrometry. Additionally, there is an enzymatic (R)-2-HG assay based on conversion of (R)-2-HG to α-KG in the presence of (R)-2-hydroxyglutarate dehydrogenase and nicotinamide adenine dinucleotide (NAD+?) and subsequent detection of generated NADH. This assay was shown to distinguish between (R)-2-HG levels in tumor tissue of patients without miDH and levels in patients with miDH-positive AML. Currently, no diagnostic or therapeutic (R)-2-HG ‘threshold’ level has been formally established; however, a discriminatory concentration of 700 ng/ml of (R)-2-HG in the serum has been proposed to identify patients with IDH mutations (serum (R)-2-hydroxyglutarate in healthy control subjects was < 200 ng/ml in this study). At (R)-2-HG levels ≥ 700 ng/ml, IDH mutations were detected that were previously missed by Sanger sequencing. Notably, the optimum compartment in which to measure (R)-2-HG has not been determined, although studies are underway to answer this question.

TREATMENT

At this writing, there are no approved selective miDH inhibitor drugs, and consistent with non-miDH myeloid malignancies, treatment decisions are based on patients’ age, performance status, use of prior treatment and other clinicopathological factors. However, the treatment landscape may soon include targeted miDH enzyme inhibitors and drugs that indirectly target miDH leukemic cells. Multiple miDH inhibitors are in preclinical stages of investigation, including HMA-101, which was shown to reduce (R)-2-HG and block colony formation in miDH1 human AML cells in vitro. AGI-026, which reduced (R)-2-HG and was associated with improved survival in a miDH2-R140 mouse model of R-2-hydroxyglutaric aciduria in vivo, and AGI-5198, which reduced (R)-2-HG and induced apoptosis of miDH1 human chondrosarcoma cells in vitro. In addition, several agents are now in various stages of clinical development (Table 3; includes ClinicalTrials.gov study registration information).

Induction chemotherapy

Induction chemotherapy has been the most commonly reported treatment for all AML patients who can tolerate such therapy, including those with miDH. Compared with patients with wtIDH, rates of response and OS for miDH patients treated with induction chemotherapy mirror general prognosis, that is, there are reports that outcomes are no different from or worse than those of patients with wtIDH or are dependent on the presence of NPM1 or other co-mutations. In a large retrospective study of patients with AML treated at a single site, patients with miDH who received remission induction or salvage chemotherapy had response rates comparable to those of patients with wtIDH regardless of co-mutational status. In contrast, in the study by Marcucci et al., patients with CN-AML and miDH1/NPM1+–FLT3-ITD– genotype had significantly shorter postinduction disease-free survival, and miDH2-R172 patients were significantly less likely to attain CR, than wtIDH patients.

Hypomethylating agents (HMAs)

Because hypermethylation is a pathogenic hallmark of miDH1/2 in myeloid malignancies, there is a theoretical rationale for treatment with an HMA. Approximately 30–50% of all AML and MDS patients who receive an HMA attain a hematological response of some type. However, evidence of increased effectiveness in patients with miDH has been equivocal. A retrospective cohort study that included 11 patients with miDH MDS revealed that hypomethylating therapy with decitabine was associated with more favorable outcomes than chemotherapy or best supportive care. In contrast, a study of 68 older patients (≥ 60 years) with de
Table 3. Drugs currently in clinical development for treatment of miDH AML and MDS

| Drug       | Mechanism of action                                                                 | Clinical phase | Patient type                                                                 | Clinical activity                                                                 | Registration       |
|------------|--------------------------------------------------------------------------------------|----------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------|
| AG-221     | Small-molecule allosteric inhibitor of miDH2 protein; reduces the oncometabolite, 2-HG | 2 and 3        | Patients with R/R AML (phase 2); older patients (≥60 years) with miDH2 R/R AML after second- or third-line therapy (phase 3) | 41% ORR in phase 1 dose-escalation and expansion study\(^70\)                    | NCT01915498       |
|            |                                                                                      |                |                                                                                 |                                                                                 |                    |
| AG-120     | Small-molecule allosteric inhibitor of miDH1 protein; reduces the oncometabolite, 2-HG | 2              | miDH1 advanced hematological malignancies                                       | 35% ORR in phase 1 dose-escalation and expansion study\(^71\)                    | NCT02044839       |
| AG-881     | Small-molecule miDH1 and miDH2 protein inhibitor; reduces the oncometabolite, 2-HG   | 1              | miDH1 and miDH2 relapsed or refractory advanced hematological malignancies—after prior miDH inhibitor failure | Unknown                                                                         | NCT02492737       |
| IDH305     | Small-molecule miDH1 inhibitor                                                      | 1              | miDH1 advanced malignancies                                                     | Unknown                                                                         | NCT02381886       |
| FT-2102    | No description available                                                             | 1/1b           | AML or high-risk MDS with miDH1; under evaluation as monotherapy and in combination with azacitidine | Unknown                                                                         | NCT02719574       |
| ABT-199    | Small-molecule BCL-2 inhibitor; works via synthetic lethality; that is, miDH cells require BCL-2 to survive | 2              | R/R AML and patients unfit for chemotherapy (reduction of BM blasts > 50%) was shown in 6/11 (54%) patients with miDH AML\(^59\) | 15.5% ORR (5/32); antileukemic activity (reduction of BM blasts > 50%) was shown in 6/11 (54%) patients with miDH AML\(^59\) | NCT02013773       |
| CB-839     | Glutaminase inhibitor                                                                 | 1              | R/R AML and older patients (≥60 years) unfit for IC (also includes patients with ALL) | Preliminary data showed 2/16 evaluable patients attained CR\(^\text{iii}\) (prespecified end point to evaluate response in miDH patients) | NCT02071927       |

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ATRA, all-trans retinoic acid; BM, bone marrow; Comb, combination; CRi, complete remission with incomplete hematological recovery; MDS, myelodysplastic syndromes; miDH, mutant isocitrate dehydrogenase; ORR, overall response rate; R/R, relapsed or refractory; 2-HG, 2-hydroxyglutarate. *ClinicalTrials.gov registration number.
Small-molecule mIDH inhibitors

Selective small-molecule mIDH1 and mIDH2 inhibitors are in clinical development. These drugs bind within the active catalytic site of mIDH enzymes and prevent the conformational change necessary for mIDH to reduce α-KG to (R)-2-HG. In preclinical studies, AGI-6780, a selective inhibitor of mIDH2-R140Q, was shown to rapidly reduce histone hypermethylation and reverse DNA hypermethylation over the course of weeks in TF-1 human erythroleukemia cells engineered to express mIDH2 protein and in IDH2-mutated primary human AML cells in vitro. Reduced methylation levels were accompanied by evidence of cellular differentiation.

AG-120, enasidenib (AG-221/CC-90007), AG-881, IDH305 and FT-2102 are small-molecule allosteric inhibitors of mIDH proteins. Both AG-120 and enasidenib have shown evidence of promoting differentiation of leukemic cells of AML patients. These drugs are not thought to be cytotoxic and may confer lower rates of aplasia, neutropenia and thrombocytopenia than traditional chemotherapeutic agents. Therefore, in theory, these agents may be optimal as salvage therapy, alone or in rational combinations, in mIDH patients with relapsed or refractory (R/R) disease.

AG-120

AG-120 is an oral inhibitor of mutant IDH1-R132 enzyme that is currently under study in a phase 1 dose-escalation and expansion trial in patients with mIDH1 advanced hematological malignancies. Plasma (R)-2-HG levels of patients with mIDH1 AML receiving AG-120 are reduced to levels seen in healthy individuals (~99.7% inhibition). AG-120 monotherapy has been generally well tolerated and associated with an ORR of 35% in a study in which the majority of patients (78%) had R/R AML.

Enasidenib

Further along in development, enasidenib is an oral inhibitor of IDH2-R140 and IDH2-R172 enzymes. Enasidenib also reduces (R)-2-HG levels in patients with mIDH2 AML to levels detected in healthy subjects. Interim results of a phase 1 dose-escalation and expansion study reported outcomes for 181 patients with advanced hematological malignancies, 128 of whom had R/R AML. ORR with enasidenib was 41%, both overall and in the subset of patients with R/R AML. There was no meaningful difference in response between R/R AML patients with IDH2-R140Q (36%) or IDH2-R172K (39%) mutations. A subgroup of patients without a demonstrable hematological response but with prolonged stable disease showed neutrophil recovery during enasidenib treatment, despite persistence of blasts in peripheral blood and/or bone marrow. Of interest, the mIDH2 VAF was not reduced in the majority of patients who attained CR on study, indicating that eradication of the mutant clone was not necessary to attain a response. A phase 2 expansion of this study is underway in patients with R/R AML, as is the phase 3 IDHentify study, which compares enasidenib with conventional care regimens. At this writing, IDHentify is enrolling older (≥60 years) patients with mIDH2 AML who are refractory to, or in relapse after, second- or third-line AML therapy. A phase 1/2 study of AG-120 or enasidenib in combination with azacitidine vs azacitidine alone in patients with mIDH1- or mIDH2-positive newly diagnosed AML is underway at this writing.

Venetoclax (ABT-199)

Venetoclax is an oral, small-molecule BCL-2 inhibitor under investigation for use in AML. Preclinical data demonstrated that expression of mIDH sensitized leukemic cells to venetoclax. This effect was mediated through the intracellular accumulation of (R)-2-HG. These preclinical findings are supported by results of recent venetoclax clinical trials in patients with AML. In a phase 2 study of single-agent venetoclax in patients with R/R AML, a CR or CR with incomplete hematological recovery was observed in 3 of the 11 (27%) patients with an IDH mutation, compared with 3 of the 21 (14%) patients without the mutation. Additionally, in a trial combining HMAs with venetoclax in elderly patients with untreated AML unfit for intensive chemotherapy, patients with an IDH mutation were more responsive. These results suggest that IDH mutations may identify a patient subgroup that is likely to respond to pharmacological BCL-2 inhibition. However, the duration of response was short for most patients, highlighting the need for combination strategies to enhance the efficacy of venetoclax.
prespecified end point to evaluate response in the subset of patients with mIDH.\textsuperscript{100}

All trans-retinoic acid (ATRA) (R)-2-HG-related inhibition of lysine-specific demethylases may promote a response to the differentiating agent, ATRA, in non-acute promyelocytic leukemia AML.\textsuperscript{101} In vitro data show that the combination of ATRA and the tyrosine kinase inhibitor, dasatinib, improved cell differentiation in primary AML samples and in AML cell lines harboring mIDH1-R132H and reduced tumor growth in mutant xenografted mice.\textsuperscript{102}

CONCLUSION

IDH mutations are frequent in myeloid malignancies, particularly AML; are uniquely associated with elevated levels of the oncometabolite, (R)-2-HG; inhibit epigenetic regulators; and should be included in AML and MDS gene panels for prognostication. Advances in understanding of the genetics underlying myeloid malignancies are igniting an exciting era of development of promising and targeted treatments. Such approaches may be more effective and less toxic than conventional chemotherapy regimens.\textsuperscript{103} Clinical trials of mIDH inhibitors as monotherapy in the R/R setting have shown much promise, although the emergence of resistant subclones has been observed.\textsuperscript{73,74} Investigations of use as front-line therapy and in combination regimens are now ongoing.

Given the genomic complexity of AML and MDS, and the observation that the founding clone can give rise to various subclones during disease evolution, selective agents that target a single mutation are unlikely to be curative in the large majority of patients. However, the use of targeted treatments in combination with drugs with non-overlapping mechanisms of action may address multifactorial pathogenic processes implicated in hematological malignancies and potentially have a revolutionary impact on patient outcomes.

CONFLICT OF INTEREST

BCM has received research funding from Celgene and Agios and has received remuneration for Advisory Board participation from Celgene and Agios. PDH is a consultant and receives clinical research funding from Celgene and declares Advisory Board participation for Agios. CDD has received research funding from Novartis, Celgene, Agios and Abbvie/Genentech and participates in Advisory Boards for Celgene and Agios. DAP has received research funding from Celgene and is a consultant for Celgene, Pfizer, Alexion, Ariad and Karyopharm. SMC has received research funding from Celgene, Agios and Abbvie/Genentech. RS declares Advisory Board participation for Novartis.

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AUTHOR CONTRIBUTIONS

All authors contributed to, revised and approved the manuscript content and gave approval for submission to the journal.

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