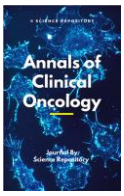

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Research Article

Diminishing oncometabolic havoc: Approved IDH1 and IDH2 inhibitors in relapsed or refractory acute myeloid leukemia

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ABSTRACT

Activating somatic mutations in isocitrate dehydrogenase (IDH) isoforms 1 and 2 in acute myeloid leukemia (AML) have been shown to contribute in wreaking intracellular oncometabolic havoc that adversely affects cellular growth and differentiation. Novel developments in IDH1 and IDH2 inhibitors have led to the recent U.S. Food and Drug Administration (FDA) approvals of these targeted agents in relapsed or refractory AML harboring these respective driver mutations. Their promising efficacy and well-tolerated toxicity profiles render them welcomed additions in the treatment landscape of AML. However, the IDH1 and IDH2 inhibitors ivosidenib and enasidenib, respectively, have unique class-effect toxicities that warrant early recognition in order for prompt management and re-institution of an otherwise effective class of agents.

1. Function of Isocitrate Dehydrogenase 1 and 2

Isocitrate dehydrogenase (IDH) isoforms 1 and 2 are nicotinamide adenine dinucleotide phosphate (NADP)-dependent enzymes involved in human cellular NADPH/NADP+ redox reactions [1]. Encoded by the *IDH1* gene on 2q33.3, IDH1 catalyzes the oxidative decarboxylation of isocitrate (ICT) to 2-ketoglutarate or α-ketoglutarate (2KG) to generate NADPH from NADP+ as well as the reverse reaction, reductive carboxylation, of 2KG to ICT that oxidizes NADPH to NADP+. In contrast to the reactions carried out by IDH1 in the cytosol and peroxsomes, IDH2, encoded by the *IDH2* gene on 15q26.1, catalyzes the same reversible reaction in the mitochondria. IDH1 and IDH2 are structural homologs and function as homodimers with roles in cellular defense against oxidative damage. Evidence is increasing to suggest that activating somatic mutations in IDH1/2 act as driver mutations across a spectrum of malignancies through gain of function, rather than loss of tumor suppression, that result in the intracellular production of the oncometabolite, (D) 2-hydroxyglutarate ((D)-2HG), which wreaks oncometabolic havoc and adversely affects several key enzymes important in cellular growth and differentiation.

IDH1/2 Mutations in AML

In acute myeloid leukemia (AML), IDH1/2 mutations are heterozygous and all known point mutations involve arginine (R) in codons 132 of IDH1(R132) and 140 or 172 of IDH2(R140 and R172) with a frequency ranging from approximately 11-20% of unselected AML cases [2-4]. IDH1 and IDH2 mutations are usually mutually exclusive, frequently occur in cytogenetically normal AML cases, and often co-occur with mutations in other genes involved in the epigenetic modification of genomic DNA [3-5]. In fact, IDH1/2 mutant expression has been shown to increase global DNA hypermethylation and inhibit TET2-induced

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cytosine 5-hydroxymethylation, DNA demethylation [4]. Additionally, IDH1(R132) and IDH2(R140) mutations frequently accompany NPM1 mutations with normal cytogenetics (but not CEBPA mutations in the case of IDH1(132)), while IDH2(R172) is often the only mutation detected in AML, when it occurs [4, 6]. Concurrent mutations in FLT3 and NRAS have also been detected only in IDH1(R132)-mutated AML [3].

IDH1/2 mutations likely affect prognosis in AML depending on the specific mutation and context in which they co-occur with other mutations [4, 7]. For example, IDH1(R132) mutations have been shown to predict poor outcome in subsets of molecular low-risk AML, whereas IDH2(R172) mutations significantly confer a worse prognosis than IDH2(R140) mutations in patients with AML [4, 7]. As such, favorable risk AML can often be defined by association with NPM1 or CEBPA mutation with neither FLT3/ITD or IDH1 mutations [6]. When IDH2 mutations occur in AML, the majority are IDH2(R140) in 80% of cases while 20% of cases are IDH2(R172) [7]. Relapse in wild-type FLT3/ITD, mutated NPM1, and mutated IDH2(R140) patients was lower than in favorable-risk cytogenetics AML patients [7]. Relapse of AML in patients with IDH2(R172) mutations but wild-type FLT3/ITD and wild-type NPM1 was comparable with adverse-risk cytogenetics [7]. In a contemporary series of IDH1/2-mutated AML patients, mutations in IDH2(140) appeared to be the most common (50%) followed by IDH1(R132) mutations (35%) and IDH2(R172) mutations (14%); IDH1/2 mutations tended to occur in older patients (median age 62, range 18-92) and less frequent therapy-related status [2]. Furthermore, remission rates by complete remission (CR) and complete remission with incomplete hematologic recovery (CRi) were 68% for those receiving induction, 42% in first salvage (S1), and 27% in second and beyond salvage (S2+) with median overall survival (OS) that was 15.4 months in induction, 8.7 months in S1, and 4.8 months in S2+ [2].

Approved IDH1/2 Inhibitors in AML

Despite many similarities of IDH1 and IDH2 mutations, it is possible that they represent distinct molecular or clinical subgroups of acute myeloid leukemia for targeting [4]. Indeed, on August 1, 2017, the U.S. Food and Drug Administration (FDA) approved the first IDH inhibitor, enasidenib, in relapsed or refractory AML based on Study AG221-C-001 [8]. In this first-in-human phase I/II trial, the oral IDH2 inhibitor was administered across 13 different dosing schedules in 239 patients with relapsed/refractory AML harboring IDH2 mutations (75% had I*DH2*-R140 mutations and 24% had *IDH2*-R172 mutations). When cytogenetics were available, 67% had intermediate risk and 33% had poor risk disease. Safety and determination of the maximum-tolerated dose (MTD) was the primary objective and based on robust steady-state drug concentrations and clinical activity, the 100 mg daily dose was selected for study expansion. In this refractory population, enasidenib was well-tolerated and achieved impressive response rates (Table 1). Overall response rate (ORR) was higher in those with *IDH2*-R172 mutations (53.3%) than *IDH2*-R140 mutations (35.4%), and the median overall survival (OS) was 9.3 months (95% confidence interval (CI) 8.2-10.9). Enasidenib-induced hyperbilirubinemia occurred in 35% of patients, and a non-dose-dependent, non-infectious leukocytosis occurred in 41 patients (17%). The FDA concurrently approved the companion diagnostic, RealTime IDH2 Assay, for detection of the IDH2 mutation.

On July 20, 2018, the FDA approved a second IDH inhibitor, ivosidenib, in IDH1-mutated relapsed/refractory AML based on Study AG120-C-001 [9]. In this phase I, multicenter, open-label study, 268 patients were enrolled, and the primary endpoints were safety, determination of the MTD, and determination of the recommended phase II dose. At 500 mg oral daily, no dose-limiting toxicities occurred and ivosidenib showed promising efficacy and a tolerable toxicity profile (Table 1). The majority of patients had intermediate-poor risk cytogenetics, and the median OS in the primary efficacy population was 8.8 months (95% CI 6.7 to 10.2). Leukocytosis of any grade was seen in 36.3% of patients. The FDA also approved the Abbott RealTi*m*e IDH1 assay for detection of IDH1 mutations.

Toxicities of Interest

The recent FDA approvals of the IDH1/2 inhibitors ivosidenib and enasidenib have afforded additional therapeutic options in the treatment paradigm of relapsed/refractory AML. As these agents are likely to undergo more widespread implementation in clinical practice, it would be prudent for clinicians to recognize the unique toxicities observed in registration trials. For example, non-infectious leukocytosis appears to be a class-effect with the majority of patients experiencing this in the first 30 days of treatment [9]. Prolongation of the QT interval was seen in 44 patients (24.6%) of patients treated with ivosidenib 500 mg daily (18 or 10.1% with grade ≥3), which resulted in dose interruptions for 13 patients (7.3%) and dose reductions in 2 (1.1%). Notably, concurrent medications known to prolong the QT were allowed in this study [9]. IDH differentiation syndrome was observed in 19 patients (10.6%) treated with ivosidenib 500 mg daily (5.0% grade ≥3), and the median time of onset of the syndrome was 29 days (range 5-59 days). No permanent treatment discontinuations resulted from this syndrome and clinical responses were still seen in those experiencing this toxicity; the recommended treatment for this syndrome was temporary holding of the drug, initiation of hydroxyurea 2-3 grams twice or three times daily, initiation of intravenous dexamethasone 10 mg every 12 hours until resolution and for at least 3 days, initiation of diuretics with furosemide as clinically indicated, and initiation of leukapharesis as clinically indicated [9]. The rate of IDH differentiation syndrome appears to be similar between ivosidenib and enasidenib [8, 9].

Table 1: FDA-approved IDH inhibitors in relapsed or refractory AML

Study	Setting	Experimental Arm	Control Arm	Efficacy	Toxicities	Ref
Enasidenib						
Study AG221-C-001	Relapsed or refractory	100 mg oral daily (n=109)	N/A	ORR 38.5%, 20.2% CR, 2.8% PR	Grade 3 AEs (safety population n=109): hyperbilirubinemia 8%, IDH-inhibitor-associated syndrome 11%, anemia 10%	[8]
Ivosidenib						
Study AG120-C-001	Relapsed or refractory	500 mg oral daily (n=125)	N/A	ORR 41.6% (95% CI 32.9-50.8%) CR/CRh 30.4% (95% CI 22.5-39.3%) CR 21.6% (95% CI 14.7- 27.8%)	Most common grade 3≥ AEs (n=179): prolonged QT interval (7.8%), IDH differentiation syndrome (3.9%), anemia (2.2%), thrombocytopenia (3.4%), and leukocytosis (1.7%)	[9]

FDA, Food and Drug Administration; IDH, isocitrate dehydrogenase; ORR, overall response rate; CR, complete response; PR, partial response; AEs, adverse events; CR/CRh, complete remission with partial hematologic recovery CI, confidence interval

Conclusion

The IDH1/2 inhibitors ivosidenib and enasidenib represent recent practice-changing approvals in the treatment of relapsed/refractory AML. In unselected patients with relapsed/refractory AML, nontargeted agents have historically produced complete remission (CR) rates of approximately 15% and median OS of <4 months [9]. To this end, they represent exciting developments in treating an otherwise poor prognosis cohort of patients with AML. These novel agents are well-tolerated though warrant special recognition of class-effect toxicities that are manageable if identified early. The future holds bright for these agents and future directions likely involve their integration into combination regimens such as integration into regimens with demethylating agents decitabine and azacitidine given the frequency of DNMT3A along with IDH1/2 mutations in AML [5, 10].

Competing Interests

None

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