Published OnlineFirst June 18, 2020; DOI: 10.1158/1078-0432.CCR-20-1820

Differentiating the Differentiation Syndrome Associated with IDH Inhibitors in AML

Joshua F. Zeidner

SUMMARY

Isocitrate dehydrogenase (IDH) inhibitors have clinical activity in acute myeloid leukemia, in part, by differentiating blasts to mature myeloid cells. In the largest systematic analysis to date, differentiation syndrome was seen in 19% of patients treated with IDH inhibitors. Early recognition with uniform diagnostic criteria, as utilized in acute promyelocytic leukemia, may reduce subsequent complications.

See related article by Norsworthy et al., p. 4280

In this issue of *Clinical Cancer Research*, Norsworthy and colleagues report findings from a systematic analysis of the incidence, risk factors, clinical characteristics, and outcomes associated with differentiation syndrome (DS) secondary to IDH inhibitors in acute myeloid leukemia (AML; ref. 1). Isocitrate dehydrogenase (*IDH*) mutations are acquired early during leukemogenesis and occur in up to 20% of patients with AML. There are two types of *IDH* mutations in AML (*IDH1* and *IDH2*) and the genomic complexity and biologic features of the disease differ within each subgroup. *IDH* mutations catalyze the aberrant production of 2-hydroxyglutarate consequently leading to a hypermethylated epigenetic phenotype and impairment of hematopoietic differentiation. In phase Ib studies, oral single-agent small-molecule inhibitors, ivosidenib and enasidenib, led to an overall response rate of 38%–40%, transfusion independence in 34%–35%, and median overall survival (OS) 8–9 months in relapsed/refractory (R/R) AML with *IDH1* or *IDH2* mutations, respectively (2, 3). Subsequently, ivosidenib and enasidenib received FDA approval for treatment of patients with newly diagnosed *IDH1*-mutated AML unfit for intensive chemotherapy, and R/R AML with *IDH1* or *IDH2* mutations, respectively. These agents dramatically advanced the treatment landscape for AML whereby oral targeted therapies are now available for patients with historically poor outcomes and limited treatment options.

On the basis of the mechanism of action of IDH inhibition, it is not surprising that these agents were shown to cause myeloid maturation and clinical signs of differentiation (**Fig. 1**). DS was first described in patients with acute promyelocytic leukemia (APL) receiving treatment with all-*trans* retinoic acid (ATRA), initially termed retinoic acid syndrome, whereby symptoms of fever, dyspnea, weight gain, hypotension, pulmonary infiltrates, and effusions are commonly observed and effectively treated with systemic corticosteroids. Since the identification of this syndrome, uniform diagnostic criteria of DS have been published (4). Early recognition and intervention decreases the rate of complications and fatal events. The Common Terminology Criteria for Adverse Events (CTCAE) now includes retinoic acid syndrome as an adverse event with severity ranging from grade 1 to 5. How to apply these diagnostic criteria to other agents that may lead to clinical signs and symptoms of myeloid differentiation in AML is unknown. DS has been an uncommon phenomenon in AML-based therapies until the development of IDH inhibitors.

The true prevalence, risk factors, and clinical outcomes of patients developing DS with IDH inhibitors has not been well established as DS was not prospectively assessed during the inception of these studies. A retrospective analysis performed by an independent differentiation syndrome review committee (DSRC) consisting of investigators who participated in the development of enasidenib revealed that DS was likely present in 11.7% of patients with R/R AML treated with enasidenib (5). After enasidenib's FDA approval, the FDA issued a warning that DS was being underrecognized and fatal events were occurring beseeching a systematic analysis and uniform diagnostic criteria.

Norsworthy and colleagues from the FDA undertook the behemoth task of defining this syndrome further. First, the investigators devised an algorithm, adapted from the Montesinos criteria in APL (4), to identify the incidence of DS in the combined 393 patients treated with either ivosidenib or enasidenib. The proposed criteria required at least two common symptoms of DS diagnosed within 7 days of one another followed by a consensus review to rule out alternative etiologies. After adjudication by the investigators, DS was identified in 19% of patients treated with ivosidenib or enasidenib, considerably higher than the incidence of DS noted in previously published studies (2, 3, 5), and slightly less prevalent than seen in APL (4). Pulmonary symptoms predominate the clinical spectrum of DS associated with IDH inhibitors. As expected, the majority had concurrent leukocytosis (ivosidenib: 79% vs. enasidenib: 61%) at the time of DS though this was not included in the proposed criteria. These features are remarkably similar to those seen in APL (4) although most of the cases were of moderate severity. In contrast to APL, however, DS was rarely seen in the first 7 days of therapy with a median of 19–20 days after treatment. Although the onset of DS should theoretically correlate with an increase in myeloid maturation, the proportion of circulating blasts at the time of DS was similar to pretreatment levels. Herein lies the clinical conundrum of establishing a diagnosis of DS versus considering alternative causes such as disease progression. These distinctions can be extremely challenging to tease out in routine clinical practice. In fact, half of the cases identified as possible DS by their algorithm were subsequently excluded after investigator adjudication.

Interestingly, several risk factors were identified as potential predictors of DS. Higher leukemia burden in the blood (≥15%–25% blasts)

Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina.

Corresponding Author: Joshua F. Zeidner, University of North Carolina, 170 Manning Drive, Houpt Building, CB #7305, Chapel Hill, NC 27599. Phone: 919-962-5164; Fax: 919-966-7748; E-mail: Joshua_Zeidner@med.unc.edu

Clin Cancer Res 2020;26:4174–6

doi: 10.1158/1078-0432.CCR-20-1820

Published OnlineFirst June 18, 2020; DOI: 10.1158/1078-0432.CCR-20-1820

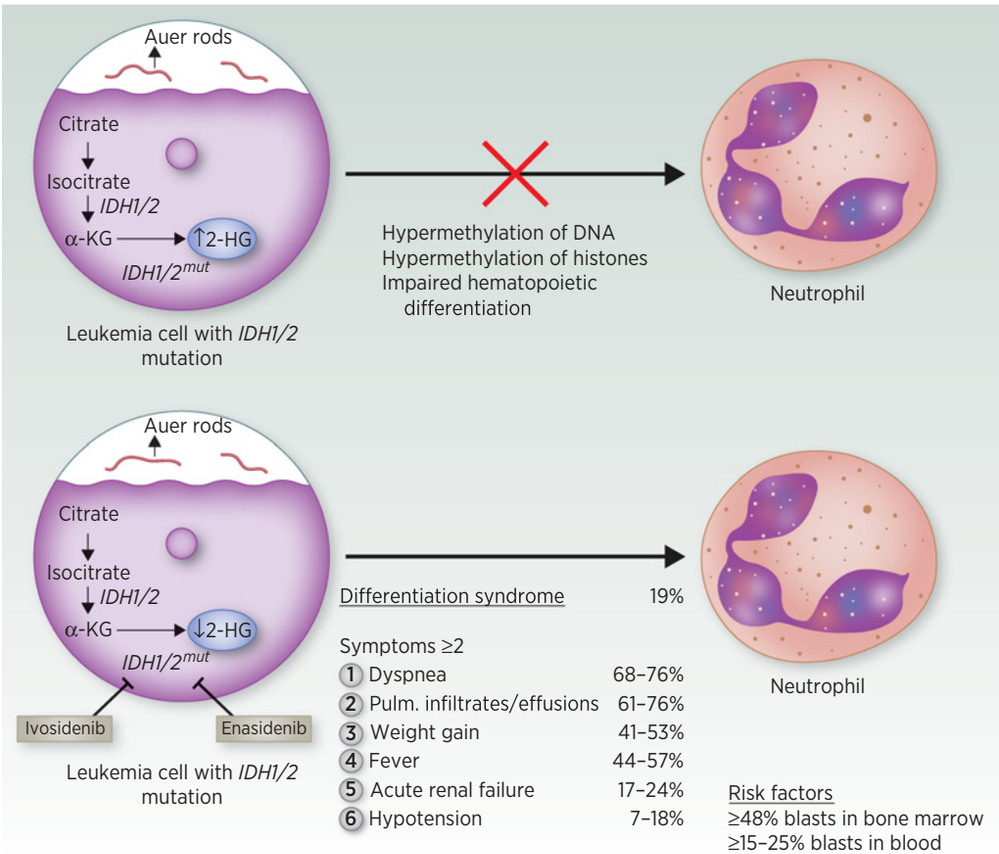

Figure 1.

IDH1 and *IDH2* catalyze the conversion of isocitrate to alpha-ketoglutarate in the cytoplasm and mitochondria, respectively. Mutations in *IDH1/IDH2* lead to the aberrant production of the oncometabolite, 2-hydroxyglutarate, in leukemia cells which leads to a hypermethylated epigenetic phenotype and impairment of hematopoietic differentiation in the leukemia cell. Ivosidenib and enasidenib are small-molecule inhibitors of mutant *IDH1* and *IDH2*, respectively. IDH inhibition decreases the production of 2-hydroxyglutarate and can restore hematopoietic differentiation and maturation. Differentiation syndrome occurs in 19% of patients treated with IDH inhibitors. α-KG, alpha-ketoglutarate; 2-HG, 2-hydroxyglutarate.

and bone marrow (≥48% blasts) prior to treatment was associated with a higher risk of DS consistent with previously published data from the DSRC (5). Concurrent mutations in *TET2* and SRSF2 were associated with higher risk of DS with ivosidenib and enasidenib, respectively, although only a proportion of patients analyzed had genomic data available for analysis. Given the small numbers of patients with DS in subset analyses, the clinical significance of these associations remains unclear and need to be further validated in a prospective fashion.

Most notably, the authors provide compelling data that DS is not associated with an improvement in clinical outcomes. Patients with ivosidenib-induced DS had lower rates of complete remission (CR)/CR with incomplete hematologic recovery (CRH: 18% vs. 36%), duration of CR/CRh (5.6 vs. 8.3 months), and median OS (4.7 vs. 10.0 months). Clinical outcomes of those with or without DS treated with enasidenib were less pronounced.

Despite the limitations of a retrospective analysis, there are several important messages from this manuscript. First, although these oral agents are relatively well tolerated and provide the opportunity for outpatient treatment, the management of IDH inhibitors is no less complex than other treatment strategies in AML. DS is relatively common in patients treated with IDH inhibitors, likely underreported, and most frequently occurs within the first 3 weeks of therapy. Early recognition and management of DS is critical. The nonspecific symptoms of DS and overlapping features of other common etiologies, such as infection and disease progression, reinforce the need for rigorous laboratory monitoring and assessment by clinicians with expertise and experience managing DS. Fortunately, fatal events were rare in these studies; however, widespread use of these agents in the community may provide a very different picture. Second, the diagnosis of DS associated with IDH inhibitors should no longer be an enigma. The clinical features of IDH inhibitor–associated DS are similar to those seen in APL which have been well annotated over the last several decades. These findings should serve as a linchpin for a uniform assessment by the Montesinos criteria (4) that should be implemented in clinical practice.

Unanswered questions remain that will need to be investigated further. What is the most effective treatment strategy for patients experiencing DS? Should we continue to extrapolate these treatment strategies from APL or are there other rational strategies that can mitigate the severity of DS? Could steroid prophylaxis, as done routinely during induction therapy for APL, decrease the incidence and severity of DS, particularly in patients at high-risk for DS? What is the impact and prevalence of DS when IDH inhibitors are combined

Published OnlineFirst June 18, 2020; DOI: 10.1158/1078-0432.CCR-20-1820

with other therapeutic agents? Needless to say, Norsworthy and colleagues take a giant leap forward in the quest to differentiate DS associated with IDH inhibitors in AML.

Disclosure of Potential Conflicts of Interest

J.F. Zeidner reports personal fees from AbbVie (independent review committee), Agios (advisory board), Daiichi-Sankyo (advisory board), Genentech (advisory board(s)), Pfizer (advisory board), Takeda (advisory board, consultancy, and institutional research funding), and AsystBio Laboratories (consultancy); grants and personal fees from Celgene (advisory Board(s), consultancy, institutional research funding) and Tolero (advisory board and institutional research funding); and grants from AROG (institutional research funding), Forty Seven (institutional research funding), and Merck (institutional research funding) outside the submitted work. No other potential conflicts of interest were disclosed.

Received May 15, 2020; revised June 1, 2020; accepted June 16, 2020; published first June 18, 2020.

References

1. Norsworthy KJ, Mulkey F, Scott EC, Ward AF, Przepiorka D, Charlab R, et al. Differentiation syndrome with ivosidenib and enasidenib treatment in patients with relapsed or refractory IDH-mutated AML: a U.S. Food and Drug Administration systemic analysis. Clin Cancer Res. 2020;26:4280–8.
2. DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med 2018;378:2386–98.
3. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood 2017;130:722–31.
4. Montesinos P, Bergua JM, Vellenga E, Rayon C, Parody R, de la Serna J, et al. Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: characteristics, outcome, and prognostic factors. Blood 2009; 113:775–83.
5. Fathi AT, DiNardo CD, Kline I, Kenvin L, Gupta I, Attar EC, et al. Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: analysis of a phase 1/2 study. JAMA Oncol 2018;4: 1106–10.

Published OnlineFirst June 18, 2020; DOI: 10.1158/1078-0432.CCR-20-1820

Clinical Cancer Research

Differentiating the Differentiation Syndrome Associated with IDH Inhibitors in AML

Joshua F. Zeidner

Clin Cancer Res 2020;26:4174-4176. Published OnlineFirst June 18, 2020.