Circulating Oncometabolite 2-Hydroxyglutarate Is a Potential Surrogate Biomarker in Patients with Isocitrate Dehydrogenase-Mutant Intrahepatic Cholangiocarcinoma

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Abstract

Purpose: Mutations in the IDH1 and IDH2 (IDH1/2) genes occur in approximately 20% of intrahepatic cholangiocarcinoma and lead to accumulation of 2-hydroxyglutarate (2HG) in the tumor tissue. However, it remains unknown whether IDH1/2 mutations can lead to high levels of 2HG circulating in the blood and whether serum 2HG can be used as a biomarker for IDH1/2 mutational status and tumor burden in intrahepatic cholangiocarcinoma.

Experimental Design: We initially measured serum 2HG concentration in blood samples collected from 31 patients with intrahepatic cholangiocarcinoma in a screening cohort. Findings were validated across 38 resected patients with intrahepatic cholangiocarcinoma from a second cohort with tumor volume measures. Circulating levels of 2HG were evaluated relative to IDH1/2 mutational status, tumor burden, and a number of clinical variables.

Results: Circulating levels of 2HG in the screening cohort were significantly elevated in patients with IDH1/2-mutant (median, 478 ng/mL) versus IDH1/2-wild-type (median, 118 ng/mL) tumors (P = 0.001). This significance was maintained in the validation cohort (343 ng/mL vs. 55 ng/mL, P < 0.0001) and levels of 2HG directly correlated with tumor burden in IDH1/2-mutant cases (P < 0.05). Serum 2HG levels > 170 ng/mL could predict the presence of an IDH1/2 mutation with a sensitivity of 83% and a specificity of 90%. No differences were noted between the allelic variants IDH1 or IDH2 in regard to the levels of circulating 2HG.

Conclusions: This study indicates that circulating 2HG may be a surrogate biomarker of IDH1 or IDH2 mutation status in intrahepatic cholangiocarcinoma and that circulating 2HG levels may correlate directly with tumor burden. Clin Cancer Res; 20(7); 1884–90. ©2014 AACR.

Introduction

Intrahepatic cholangiocarcinoma represents a unique clinical entity with significant challenges. As a subset of biliary tract cancers, it represents the second most common form of liver malignancy, and incidence as well as mortality rates have steadily increased (1). Surgical resection represents the only curative treatment. However, only 10% to 20% of patients present with early-stage disease that is amenable to curative surgery (1, 2). Even with the standard treatment of gemcitabine and cisplatin combination chemotherapy, the median survival of patients with locally advanced or metastatic disease remains less than 1 year (3). Therefore, molecularly targeted therapies may provide an important means of improving patient outcomes.

Our understanding of the molecular mechanisms underlying the pathogenesis of intrahepatic cholangiocarcinoma has been expanding (4, 5). Recently, mutations in the genes encoding for isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) have been identified as a significant molecular feature in approximately 20% of intrahepatic cholangiocarcinoma cases (6–8). The prevalence of this genetic signature may suggest an important pathophysiological mechanism in intrahepatic cholangiocarcinoma, which may offer novel...
Translational Relevance

Mutations in the IDH1 and IDH2 (IDH1/2) genes represent a new genetic signature in intrahepatic cholangiocarcinoma. Although accumulation of 2-hydroxyglutarate (2HG) has been previously detected in the tumor, it remains unknown whether IDH1/2 mutations can lead to high levels of 2HG circulating in the blood. Our exploratory study has provided evidence that elevated circulating levels of 2HG in patients with IDH1/2-mutant intrahepatic cholangiocarcinoma may serve as a surrogate biomarker of IDH1/2 mutation status in patients with intrahepatic cholangiocarcinoma. Furthermore, preliminary evidence of circulating 2HG correlating with tumor burden further indicates the potential for evaluating serum 2HG as a pharmacodynamic biomarker of treatment response in patients with IDH1/2-mutant intrahepatic cholangiocarcinoma.

Insights on how to develop targeted approaches against this treatment-refractory disease.

IDH1 and IDH2 (IDH1/2) normally function to catalyze the oxidative carboxylation of isocitrate to α-ketoglutarate. The recurrent cancer mutations in these enzymes confer neomorphic activity through the reduction of α-ketoglutarate to the metabolite R(-)-2-hydroxyglutarate (2HG), resulting in 2HG accumulation in the tumor tissue (9, 10). High intracellular levels of 2HG have recently been shown to be sufficient for promoting the tumorigenic effects of mutant IDH activity that are associated with enhanced proliferation and impaired differentiation (11).

Although elevated levels of circulating 2HG have been identified in the blood of patients with IDH1/2-mutant acute myeloid leukemia (AML) (12–14), the clinical utility of circulating 2HG has not yet been clearly established in solid tumors (15). This has partly been hampered by the prevalence of IDH1/2 mutations confined primarily to a small number of cancer types, which is then further limited when considering a relatively rare malignancy such as intrahepatic cholangiocarcinoma. We have previously identified elevated levels of 2HG in the tumor tissue of IDH1- and IDH2-mutant intrahepatic cholangiocarcinoma (6). Because 2HG has been shown to be a membrane-diffusible metabolite (9, 10, 16), it is of interest to determine whether 2HG can be detected in the serum of patients with intrahepatic cholangiocarcinoma carrying a somatic IDH1 or IDH2 mutation. Accurate detection and quantification of serum 2HG could potentially serve as an efficient and less-invasive method of assessing a patient’s response to IDH-targeted therapies, once promising drugs currently undergoing preclinical evaluation enter into clinical testing (17, 18). In this study, we therefore sought to characterize serum 2HG levels as a biomarker of IDH1/2 mutational status and its association with tumor burden in IDH1/2-mutant intrahepatic cholangiocarcinoma tumors.

Patients and Methods

Patients and samples

An initial screening cohort consisted of 31 patients diagnosed with intrahepatic cholangiocarcinoma that were treated at the Massachusetts General Hospital (Boston, MA) from 2008 to 2012. Subjects were selected based on the availability of tumor mutational profiling (performed as part of their clinical management) and paired blood samples (collected previously with informed consent for research banking purposes). However, many of the banked blood samples available for this cohort were obtained after the initiation of treatment. To increase the number of evaluable samples and to overcome any bias associated with obtaining blood samples after treatment, a second validation cohort from Queen Mary Hospital at The University of Hong Kong (Hong Kong, China) was evaluated. This group consisted of 38 patients with blood samples that were collected before tumor resection and treatment. Tumor burden measurements were recorded for each patient in the validation cohort based on linear dimensions measured along perpendicular axes from resected tumors. The tumor volume was calculated using an ellipsoid formula. Clinical data were extracted from patient records, including age, grade, stage, treatment, recurrence, and survival. Institutional review board approval was obtained for this study.

Genotype analysis

Mutational profiling was performed using nucleic acids that were extracted from resected intrahepatic cholangiocarcinoma tumor tissue for each patient. Specific hotspot mutations in the IDH1 gene at nucleotide positions c.394 and c.395 (amino acid position p.R132) were identified using a multiplexed mutational profiling platform that has been previously described and clinically implemented (6, 19). Rare IDH1 mutations that have been reported in other tumor types were not evaluated (20). Sanger sequencing was used to identify mutations in the IDH2 gene at exon 4 (including mutations at codons p.140 and p.172) using methods and PCR primers that have been previously reported (6). Labeled PCR products were separated using an ABI PRISM 3730 DNA Analyzer, and the data were interpreted with GeneMapper Analysis Software (Life Technologies; Applied Biosystems).

Circulating 2HG analysis

Serum was isolated from whole blood, aliquoted, and stored at −80°C until analysis. Circulating levels of 2HG were measured at Agios Pharmaceuticals using liquid chromatography/tandem mass spectrometry (LC-MS/MS) analysis (AB Sciex 4000) operating in negative electrospray mode. Multiple-reaction monitoring (MRM) data were acquired for each compound using the following transitions: 2HG (146.9/128.8 amu), 13C5-2HG (151.9/133.8 amu), and 3HMG (160.9/152.9 amu). Chromatographic separation was performed using an ion-exchanged column (BioRad Fast Acid analysis; 9 μm, 7.8 × 100 mm; Bio-Rad). The flow rate was 1 mL/min of 0.1% formic acid in water with a
total run time of 4 minutes. Thirty microliters of sample was extracted by adding 30 μL of internal standard in water followed by 200 μL of acetonitrile. The sample was vortex mixed, centrifuged, and 100 μL of supernatant transferred to a clean 96-well plate. The supernatant was diluted with 100 μL of deionized water and 25 μL injected on column.

Statistical analysis
The comparison of biomarkers with respect to IDH1/2 mutational status or study site was performed using the exact Mann–Whitney–Wilcoxon test. Median and interquartile ranges are provided as descriptive statistics. Correlations were quantified as Spearman correlation coefficients and tested with the Spearman test. \( P \) values of <0.05 were considered statistically significant.

Results
Patient characteristics
The patient characteristics of the screening and validation cohorts are summarized in Table 1. A total of 31 patients diagnosed with intrahepatic cholangiocarcinoma with clinically determined IDH1 and IDH2 gene mutational status, and with available banked whole blood, comprised the screening cohort. The median age of this group was 57 years, and approximately 65% of these patients presented with stage IV disease. These characteristics are consistent with patients that normally undergo clinical mutational profiling in an effort to identify alternative treatment courses after failing standard of care.

To expand analysis of patients with intrahepatic cholangiocarcinoma, a second validation cohort consisting of 38 patients with intrahepatic cholangiocarcinoma who underwent surgical resection was then identified and retrospectively genotyped to identify IDH1/2 mutations. The age, sex, and CA19-9 blood levels of this validation cohort were comparable with those in the screening cohort (Table 1). However, the validation group patients spanned early disease stages, including stage I (50%), stage II (~13%), and stage III (37%), and did not include stage IV patients.

IDH1 and IDH2 mutational status
In the screening cohort, IDH1 mutations were found in 11 of 31 patients with intrahepatic cholangiocarcinoma, for an overall incidence of 35%. These included point mutations in IDH1 p.R132C (n = 7), p.R132L (n = 3), and p.R132G (n = 1; Table 2 and Supplementary Table S1). No IDH2 mutations were identified. The intrahepatic cholangiocarcinoma–resected tumor samples from the validation cohort were genotyped using the same clinical genotyping platform. We identified mutations in IDH1 in 4 of 38 patients (10%) and IDH2 in 3 of 38 patients (8%), for a combined frequency of IDH1/2 mutations in 18% of the cohort. The point mutations included IDH1 p.R132C (n = 2) and p.R132L (n = 2), as well as IDH2 p.R172W (n = 2) and p.R172K (n = 1). The frequency of IDH1 mutations was statistically higher in the screening cohort, and the frequency of IDH2 mutations was significantly greater in the validation cohort (\( P = 0.04 \)). It is not certain whether these differences are related to regional differences or the distinct tumor stage characteristics between the two cohorts. Unlike what has been previously reported (7), there was no correlation between the presence of IDH1/2 mutations and either the grade of tumor or the histologic clear-cell changes (Table 3).

Circulating 2HG levels and correlation with tumor burden
For our screening cohort, blood had been obtained from patients with intrahepatic cholangiocarcinoma at variable times in regard to the initiation and response to treatment. For patients with a somatic IDH1/2 mutation, the radiological tumor burden and response to therapy at the time of 2HG measurement are listed in Supplementary Table S2. Despite the very different blood sampling schedules, serum 2HG levels were still detected at significantly elevated levels in IDH1-mutant (median, 478 ng/mL; interquartile range, 174–643 ng/mL) versus IDH1–wild-type patients with intrahepatic cholangiocarcinoma (median, 118 ng/mL; interquartile range, 68–160 ng/mL; \( P < 0.001 \); Fig. 1). There were only two IDH1-mutant patients with 2HG levels less than 170 ng/mL in the screening cohort, in which blood was obtained after a clinical response to treatment (Table 2). The first of these 2 patients (R25) had resected stage II intrahepatic cholangiocarcinoma, in which the blood sample was obtained about 2 months postoperatively with no evidence of disease. The second patient (R14) had stage IV intrahepatic cholangiocarcinoma in which the blood sample was obtained 6 months after receiving gemcitabine, oxaliplatin, and panitumumab on clinical study and when a partial radiologic response was documented. The ability to detect

| Table 1. Characteristics of patients with intrahepatic cholangiocarcinoma across cohorts |
|---------------------------------|-----------------|-----------------|
| **Characteristics** | **Screening cohort** | **Validation cohort** |
| Total number of cases | 31 | 38 |
| Age at diagnosis (y) | | |
| Median | 57 | 64 |
| Range | 36–78 | 25–79 |
| Sex | | |
| Male | 17 | 22 |
| Female | 14 | 16 |
| Baseline CA19-9 level (U/mL) | | |
| Median | 34 | 34 |
| Range | <1–3,175 | <2–7,520 |
| Unknown | 5 | 18 |
| Stage of disease at diagnosis | | |
| I | 4 | 19 |
| II | 4 | 5 |
| III | 3 | 14 |
| IV | 20 | 0 |
data combined indicate that a threshold of serum 2HG set at
intrahepatic cholangiocarcinoma in a clinical setting. These
between 2HG levels in patients with
(Fig. 1). Surprisingly, there were no notable differences
of identifying
0.68), supporting the robustness of 2HG as a potential means
hepatic cholangiocarcinoma across the two cohorts (P =
interquartile range, 192–596 ng/mL) versus
P
½
< 0.0001) patients with intrahepatic cholangiocarcinoma
(Fig. 1). Surprisingly, there were no notable differences
2HG levels in the validation cohort were also signif-
ance of metastatic disease and an incomplete
response to treatment.
To address the limitations of evaluating 2HG in samples
drawn after treatment initiation, a second validation cohort
was pursued in which all blood samples were collected before
surgical resection and chemotherapy treatment (n = 38). The
serum 2HG levels in the validation cohort also were signifi-
cantly elevated in the IDH1/2-mutant (median, 343 ng/mL;
interquartile range, 192–596 ng/mL) versus IDH1/2-wild-
type (median, 55 ng/mL; interquartile range, 42–82 ng/mL;
P < 0.0001) patients with intrahepatic cholangiocarcinoma
(Fig. 1). Surprisingly, there were no notable differences
between 2HG levels in patients with IDH1/2-mutant intra-
hepatic cholangiocarcinoma across the two cohorts (P =
0.68), supporting the robustness of 2HG as a potential means
of identifying IDH1/2-mutant versus wild-type patients with
intrahepatic cholangiocarcinoma in a clinical setting. These
data combined indicate that a threshold of serum 2HG set at
>170 ng/mL can discriminate the presence of an IDH1/2-
mutant from an IDH1/2-wild-type intrahepatic cholangio-
carcinoma tumor using patient blood, with a sensitivity of
83% and a specificity of 90%. Within the context of our
limited cohort size and using the Cox proportional hazards
model, baseline 2HG was not found to be predictive of
overall survival or recurrence-free survival in the validation
cohort (P = 0.737 and 0.756, respectively).
Although in vitro differences have been reported (21), it
has not been clearly established whether the various mutant
forms of IDH1 or IDH2 can produce variable levels of 2HG
in vivo. When evaluating blood collected across all of our
patients with intrahepatic cholangiocarcinoma, albeit a
limited sample size, there were no significant differences
in the levels of circulating 2HG in patients with a tumor
mutant for IDH1 versus IDH2 (P = 0.29). However, the high
variability that we noted in circulating 2HG levels across
the IDH1/2-mutant patients with intrahepatic cholangio-
carcinoma could have reduced the ability to identify more subtle
differences. This also raised the question of whether the

| Table 2. Characteristics of patients with IDH1-mutant or IDH2-mutant intrahepatic cholangiocarcinoma |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Patient ID     | IDH1 or IDH2 mutation | Serum 2HG (ng/mL) | CA19-9 (U/mL) | Stage | Sex | Age |
|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Screening cohort |
| R9             | IDH1c.394C>G (p.R132G) | 1,093          | 653            | IV | F | 56 |
| R10            | IDH1c.394C>T (p.R132C) | 173            | n/a           | IV | M | 48 |
| R11            | IDH1c.394C>T (p.R132C) | 174            | n/a           | IV | M | 58 |
| R14            | IDH1c.394C>T (p.R132C) | 97             | <1            | IV | M | 46 |
| R23            | IDH1c.394C>T (p.R132C) | 330            | 24            | IV | F | 51 |
| R25            | IDH1c.394C>T (p.R132C) | 107            | n/a           | II | F | 64 |
| R26            | IDH1c.394C>T (p.R132C) | 509            | 19            | IV | M | 64 |
| R27            | IDH1c.394C>T (p.R132C) | 25,570         | 74            | IV | M | 56 |
| R22            | IDH1c.395G>T (p.R132L) | 500            | 35            | IV | F | 60 |
| R4             | IDH1c.395G>T (p.R132L) | 777            | 382           | IV | F | 77 |
| R20            | IDH1c.395G>T (p.R132L) | 478            | n/a           | IV | F | 42 |
| Validation cohort |
| P14            | IDH1c.394C>T (p.R132C) | 174            | 45            | I  | M | 56 |
| P15            | IDH1c.394C>T (p.R132C) | 545            | 11            | II | F | 50 |
| P3             | IDH1c.395G>T (p.R132L) | 108            | 2.0           | I  | M | 70 |
| P30            | IDH1c.395G>T (p.R132L) | 343            | n/a           | I  | F | 76 |
| P2             | IDH2c.S14A>T (p.R172W) | 211            | n/a           | I  | F | 55 |
| P36            | IDH2c.S14A>T (p.R172W) | 648            | n/a           | I  | F | 57 |
| P23            | IDH2c.S15G>A (p.R172K) | 1,212          | n/a           | I  | F | 73 |

IDH1/2 mutational status | Number of cases | Clear-cell change | Grade of tumor |
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<tbody>
<tr>
<td>IDH1/2 mutant</td>
<td>7</td>
<td>0 (0%)</td>
<td>Grade 1: 1 (14%)</td>
</tr>
<tr>
<td>IDH1/2 wild-type</td>
<td>26</td>
<td>7 (27%)</td>
<td>Grade 1: 4 (15%)</td>
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wide range of circulating 2HG could be attributed to differences in tumor burden. Because all blood samples from the validation group were collected before surgical resection, levels of circulating 2HG levels were evaluated relative to tumor volume (Supplementary Table S3). Although tumor weight was not recorded, tumor linear dimensions measured along perpendicular axes from these resected tumors were recorded and the tumor volume was calculated using an ellipsoid formula. As shown in Fig. 2, 2HG levels indeed correlated directly with tumor burden (Spearman $\rho$, 0.89; $P = 0.0123$) in patients with IDH1/2-mutant intrahepatic cholangiocarcinoma.

Discussion

The treatment of advanced intrahepatic cholangiocarcinoma remains an unmet need, where new strategies are desperately needed. In this study, we confirmed an increasing body of evidence that intrahepatic cholangiocarcinomas have a relatively high frequency of IDH1 and IDH2 mutation (6–8). Newly developed IDH1 and IDH2 inhibitors have shown early evidence of activity in preclinical studies using IDH1-mutant glioma and IDH2-mutant leukemic model systems, respectively (17, 18), and suggest a potentially viable treatment strategy in intrahepatic cholangiocarcinoma. As these IDH-targeted therapies begin to enter early clinical testing, there will be a need for robust pharmacodynamic markers that can be used to evaluate on-target drug effects.

There have been tremendous advances in our understanding of how mutants IDH1 and IDH2 drive the tumorigenic process (22). It has recently been demonstrated that 2HG in itself is sufficient to disrupt differentiation and promote growth factor independence in leukemic cells (11). Therefore, 2HG may very well be the primary oncogenic effector of mutants IDH1 and IDH2 activity. The intracellular accumulation of this metabolite has been shown to disrupt normal functioning of multiple $\alpha$-ketoglutarate–dependent dioxygenases (23). Key targets include tet methylcytosine dioxygenase 2 (TET2) and jumonji domain–containing proteins that function in epigenetic regulation, likely serving as the primary mechanisms of aberrant DNA and histone methylation that has been identified in IDH-mutant tumors (11, 17, 23–28). Another target of 2HG is the EglN prolyl 4-hydroxylases that promote proteasomal degradation of the hypoxia-inducible factor transcription factor (11, 24, 29). Given the diversity of these mechanisms, it will be of interest in determining the precise role of 2HG in driving the carcinogenic process in intrahepatic cholangiocarcinoma.
The neomorphic activity of mutants IDH1 and IDH2 in the production of the cell-permeable 2HG oncometabolite lends itself for use as a circulating biomarker. AML has so far provided the model of how 2HG can be used to monitor treatment effects and disease activity. Levels of 2HG in the serum and urine of patients with IDH1- or IDH2-mutant AML have been found to decrease throughout the course of conventional therapy, in a manner concordant with decreases in blast counts (13). Furthermore, the inability to achieve a normal level of serum 2HG at remission has been associated with worse overall survival in AML (12).

Given the rarity of intrahepatic cholangiocarcinoma relative to AML, there is difficulty in obtaining the sufficient patient samples for meaningful evaluation, and our study reports on a collaborative effort between two institutions in which samples were collected over several years. Unlike what has been recently reported in glioma (15), we have identified for the first time a correlation between circulating 2HG and tumor IDH mutation status in a solid tumor. Not surprisingly, the concentration of blood 2HG was significantly lower in patients with IDH-mutant intrahepatic cholangiocarcinoma (i.e., a solid tumor) compared with what has been reported in patients with IDH-mutant AML (i.e., a blood malignancy; refs. 12, 13). From our small cohort analysis, a threshold of circulating 2HG levels >170 ng/mL could predict the presence of an IDH1/2 mutation in a patient with intrahepatic cholangiocarcinoma with a sensitivity of 83% and a specificity of 90%. We have also provided preliminary data suggesting a correlation between circulating 2HG levels and tumor burden in IDH1-mutant cholangiocarcinoma, raising the question about whether serial 2HG monitoring in the blood can serve as a potential surrogate marker of treatment response in IDH1-mutant cholangiocarcinoma. Although this study is an important first step, larger prospective studies are needed to confirm the relationship between levels of circulating 2HG and tumor burden. Furthermore, it is unknown whether serum 2HG can serve as a prognostic marker for patients with IDH1- or IDH2-mutant cholangiocarcinoma.

In summary, our study suggests that circulating 2HG may serve as a surrogate biomarker of IDH1 or IDH2 mutation status in intrahepatic cholangiocarcinoma that is related to tumor burden. Future studies will be needed to determine how well 2HG correlates with changes in tumor volume over the course of treatment. With the highly anticipated entrance of new IDH1- and IDH2-targeted therapies in early-phase clinical trials, it will be of interest to determine the utility of 2HG as a pharmacodynamic marker of treatment response in patients with IDH-mutant intrahepatic cholangiocarcinoma.

Disclosure of Potential Conflicts of Interest
D. R. Borger, A. J. Iafrate, and L. W. Ellisen are consultants/advisory board members for Bio-Reference Laboratories, Inc. K. Straley and D. P. Schenkein are employees of and have ownership interest in Agios Pharmaceuticals. S. Agresta is an employee of Agios Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

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