Review Article

Therapeutic inhibition of isocitrate dehydrogenase mutations in glioma and cholangiocarcinoma: new insights and promises—a narrative review

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Background and Objective: The identification of mutation hot spots in the isocitrate dehydrogenase (IDH) genes is one of the most important cancer genome-wide sequencing discoveries with relevant impact in the treatment of some orphan tumors. These genes were mostly found mutated in lower-grade gliomas (LGGs), acute myeloid leukaemia (AML), myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs) and in cholangiocarcinoma. This aberrant genomic condition represents a therapeutic target of great interest in cancer research, especially in AML, given the limitations of currently approved therapies in this field. In this review, we investigate the role of IDH mutation and the mutant IDH (mIDH)-targeted therapies for cholangiocarcinoma and glioma.

Methods: Here, we provide an overview of the IDH mutation role and discuss its role in tumorigenesis and progression of some solid cancers, in which the therapeutic strategy can be completely changed thanks to these brand-new therapeutic options.

Key Content and Findings: The encouraging early clinical data demonstrated to be a proof of concept for investigational mIDH1/2 inhibitors in tumors with a paucity of therapeutic possibilities.

Conclusions: Moreover, we list the most important randomised clinical trials still active with their preliminary results.

Keywords: Isocitrate dehydrogenase mutation (IDH mutation); orphan solid tumors; IDH inhibitors; lower-grade gliomas (LGGs); cholangiocarcinoma

Submitted Feb 14, 2024. Accepted for publication Jul 19, 2024. Published online Aug 21, 2024.
doi: 10.21037/cco-24-17
View this article at: https://dx.doi.org/10.21037/cco-24-17

Introduction

Recent progress in cancer genetics have tried that hot-spot mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2 may occur in lower-grade gliomas (LGGs), acute myeloid leukaemia (AML), intrahepatic cholangiocarcinoma (iCCA), chondrosarcoma, and thyroid carcinomas (1-8). Particularly, IDH2 mutations are also frequently evidenced in rare malignancies, such as angioimmunoblastic T-cell lymphoma and solid papillary carcinoma with reverse polarity (SPCRP) (9,10). Less frequently, these molecular

Table 1 Clinical trials of IDH1/2 inhibitors

Trial	Treatment	Phase	Setting	Status
NCT02746081	BAY-1436032	I	Advanced tumors, IDH1 mut	Active, not recruiting
NCT02492737	Vorasidenib (AG-881)	I/II	Advanced hematologic malignancies IDH1 and/or IDH2 mut	Completed
NCT02481154	Vorasidenib (AG-881)	I/II	Advanced tumors IDH1/2 mut (CCA, chondrosarcoma, glioma IDH172 mut)	Active, not recruiting
NCT04164901	Vorasidenib (AG-881)	III	Advanced malignancies IDH1r132	Active, not recruiting
NCT02074839	Ivosidenib (AG-120)	I/II	Advanced hematologic malignancies with IDH1 mutation	Recruiting
NCT02073994	Ivosidenib	I/II	Advanced solid tumors (CCA, chondrosarcoma, glioma)	Active, not recruiting
NCT03471260	Ivosidenib + venetoclax + azacitidine	I/II	Advanced malignancies with IDH1 mutation	Active, not recruiting
NCT03173248	Ivosidenib + azacitidine	III	AML with IDH1 mutation	Recruiting
NCT01915498	Enasidenib (AG-221)	I/II	Advanced hematologic malignancies with IDH2 mutation	Active, not recruiting
NCT02273739	Enasidenib (AG-221)	I/II	Advanced solid tumors (glioma, iCCA, angioimmunoblastic T-cell lymphoma, chondrosarcoma IDH2 mut)	Completed
NCT02381886	IDH 305	I/II	Advanced malignancies IDH1R132	Active, not recruiting
NCT04056910	Ivosidenib + nivolumab	II	Advance tumors IDH1/2 mut	Recruiting
NCT02428855	Dasatinib	II	Advanced iCCA IDH1/2 mut	Completed
NCT03878095	Olaparib + ceralasertib	II	Advanced tumors IDH1/2 mut	Suspended
NCT04521686	LY3410738	I	Advanced solid tumor IDH1 mut (glioma, CCA, chondrosarcoma, CCA, IDH2 mut)	Active, not recruiting

IDH, isocitrate dehydrogenase; mut, mutant; CCA, cholangiocarcinoma; AML, acute myeloid leukemia; iCCA, intrahepatic cholangiocarcinoma.

alterations are reported in prostate tumors, paraganglioma, and melanoma (11-13). In particular, IDH2 mutation has been found recovered also in carotid body paragangliomas, a rare neuroendocrine tumor. This mutation may play a role in tumorigenesis of these tumors and could be used as a therapeutic target (14). IDH mutations occur frequently in chondrosarcoma, however, its prognostic role as well as therapeutic potential remain unclear (15,16). IDH mutation appears to play a central role in the establishment and maintenance of cancer stem cells (17).

The role of IDH mutation in cancer progression relies on its physiological function. As well established in literature evidence, IDH mutations, usually localised at the arginine residue (R132 for IDH1, R140, or R172 for IDH2), are somatic heterozygous and missense point mutations. The IDH mutated genes produce 51 the oncometabolite D-2-hydroxyglutarate (D-2HG) (18), thus inhibiting α-ketoglutarate (αKG)-dependent dioxygenases involved in the control of epigenetics and cellular growth and normal differentiation processes, in a manner that likely promotes leukemogenesis and tumorigenesis (19-21).

Therefore, intensive efforts have been conducted to identify small molecules with the ability to inhibit mutant IDH (mIDH) enzymes for the development of IDH-directed anti-cancer therapy (*Table 1*).

In this regard, clinical results from randomised clinical trials showed the undoubtedly benefit gained in IDH-mutated LGG and cholangiocarcinoma with the use of anti-IDH targeted therapies (22-24). Unfortunately, nowadays, the use of these drugs is still not authorised in many countries due to local legislation.

Hence, in this review, we discuss the cancer-related role of IDH mutation and the results of mIDH-targeted therapies in the context of cholangiocarcinoma and gliomas highlighting promising developments, unanswered questions, and important future directions about this therapeutic approach. We present this article in accordance with the Narrative Review reporting checklist (available at https://cco.

Table 2 The search strategy summary regarding IDH1 and IDH1 mutation

Items	Specification
Date of search	23/July/2023
Database searched	PubMed
Search terms used	IDH1 mutation, IDH2 mutation, resistance mechanisms to IDH1/2 mutations, glioma, cholangiocarcinoma
Timeframe	2009–2023
Inclusion criteria	All phase 2 and 3 trials, specific articles deal with IDH1 and 2 mutation and all selected articles in English are included
Selection process	By all the authors, there is no need consensus because we find all in already published article

IDH, isocitrate dehydrogenase.

amegroups.com/article/view/10.21037/cco-24-17/rc).

Methods

We conducted a narrative review regarding the IDH1 and 2 mutations including the specific mutation and acquired resistance. In particular, we developed a research about the role of IDH1 and 2 mutation in cholangiocarcinoma and glioma tumors. We used the keywords: IDH1 mutation, IDH2 mutation, cholangiocarcinoma, glioma and resistance mechanisms to IDH1/2 mutations, filtered for last ten years and restricted to clinical trial, randomized trial and review and meta-analysis We used the PubMed searching system (*Table 2*).

An actionable mutation

Strength and limits

IDH1 resides in the cytosol, whereas IDH2 is located in the mitochondria. Despite their distinct cellular locations, both isozymes facilitate the reversible oxidative decarboxylation of isocitrate to αKG while simultaneously reducing $NADP^+$ to NADPH. Through biochemical analyses, it has been observed that mIDH enzymes exhibit a neomorphic activity.

Specifically, they convert αKG into the oncometabolite D-2HG in a process that deviates from the norm by consuming NADPH rather than producing it, and concurrently generating $NADP^+$ (25). The prognostic role of IDH1(R132) mutation is associated with reduced $NADP^{+-}$ dependent IDH activity in glioblastoma (25,26).

Physiologically, IDH is implicated in a range of cellular processes that go beyond metabolism to encompass epigenetic regulation, redox balance, and DNA repair mechanisms. One of the reaction products, αKG, serves as a cofactor for various enzymes collectively known as αKG-dependent dioxygenases. This group includes ten eleven translocation hydroxylases (TET), Jumonji c-domain containing lysine demethylase (KDMs), prolyl-hydroxylases domain-containing (PHD), factor inhibitor of HIF (FIH), and αKG-dependent-dioxygenase homologs (ALKBH) (27). TET family enzymes are involved in 5-methyl cytosine hydroxylation, while KDMs contribute to DNA and histone demethylation. These processes are pivotal for cell differentiation, influencing whether certain genes are expressed based on contextual transcriptional regulation (28).

The exact mechanism through which IDH mutations contribute to cancer pathogenesis remains uncertain, despite significant understanding of their biological impact. These effects are largely attributed to the structural resemblance between D-2HG and αKG, where the only distinction lies in the oxidation state of the carbon-2 position. This structural similarity leads to competitive inhibition, particularly among the extensive family of αKG-dependent dioxygenases, numbering over 70. Consequently, pathways utilizing αKG as a substrate are disrupted in IDH-mutant cancers. This disruption results in epigenetic dysregulation, marked by abnormal histone and DNA methylation, chromatin reorganization, hindered cellular differentiation, and other transformative effects (29-39).

Missense mutations, almost always heterozygous, in the IDH1 Arg132 codon cause a single amino acid substitution, most commonly to histidine (IDH1-R132H), but also to cysteine, serine, glycine, leucine, or isoleucine (7,12). Missense mutations in IDH2 codon for Arg140 or Arg172 (homologous to IDH1R132) occur predominantly as IDH2R140Q or IDH2R172K substitutions, although other amino acid changes occur (40,41). The common

function of IDH1/2 active-site mutations is a neomorphic enzyme activity that catalyzes the conversion of αKG to D-2HG (18). Under physiological conditions, cellular D-2HG accumulation is limited due to the actions of the endogenous D-2HG dehydrogenase (D2HGDH), which catalyzes the conversion of D-2HG to αKG. However, the neomorphic activity of mIDH causes D-2HG to accumulate to supraphysiological levels within cells. Elevated D-2HG concentrations can be detected in the serum of patients with IDH-mutant AML and in IDH-mutant gliomas in patients (6,26,42-44). Elevated D-2HG levels in tumour tissues may provide a clinically useful biomarker for the non-invasive detection of IDH mutations due to the low background of D-2HG in normal tissue and almost invariable upregulation of D-2HG in the context of IDH active site mutations (45).

We can identify the most frequent *IDH1* mutation with the help of immunohistochemistry using the anti-IDH antibody that recognises the R132H mutated protein. Less frequent *IDH1* and *IDH2* mutations can only be identified by DNA sequencing. IDH1 immunohistochemistry can be performed on fixed and paraffin embedded tissue samples. Concerning about cholangiocarcinoma, immunohistochemistry (IHC) positive mutations of IDH1 are not sufficient, but need next generation sequencing (NGS) or protein chain reaction (PCR) confirmation before starting a target therapy.

In situations where immunohistochemistry results are negative or inconclusive, especially in lower-grade tumors or suspected secondary glioblastomas, direct sequencing of *IDH1* and *IDH2* genes using PCR- or NGS-based methods should be carried out to screen for non-IDH1-R132H mutations. Non-invasive methods to detect the IDH mutation are being developed, including detection of the IDH1 mutation in plasma by digital PCR and magnetic resonance spectroscopy which allows the detection of abnormal accumulation of 2-hydroxyglutarate within the tumor, which could potentially help IDH mutation monitoring and therefore response to treatment (46,47). IDH1/2 RGQ PCR kits currently most used are Therascreen® (Redwood, CA, USA) and Entrogen® (Woodland Hills, CA, USA).

The epigenetic disruption caused by IDH1/2 mutant enzymes results in increased methylation of histones and DNA in a manner dependent on cell passage. This phenomenon is evident in the methylation profiles of various human malignancies, where tumors with IDH1/2 mutations exhibit a distinctive CpG island methylator phenotype. This phenotype is characterized by a significant level of DNA hypermethylation in CpG-rich regions (48). It has shown to both glioma and AML, epigenetic dysregulation caused by elevated D-2HG levels is reported to induce a DNA hypermethylation phenotype, which is clinically associated with increased methylation of patient tumor DNA and with the glioma-associated CpG island hypermethylated phenotype (GCIMP) (34,39,45-51). Several experimental and clinical data indicate that D-2HG-induced dysregulation of histone and DNA methylation suppress physiological cellular differentiation processes (35,52,53). Consequently, inhibition of cellular differentiation by D-2HG is thought to promote the pathological self-renewal of stem-like progenitor cells, which may create a cellular state that is permissive to malignant transformation. In addition to inhibiting αKG dependent dioxygenase enzymes, D-2HG has also been reported to activate, directly or indirectly, a number of enzymes and pathways (54-56). For example, D-2HG has been activated the prolyl hydroxylase egg-laying defective nine (EGLN) (55). Interestingly, this activation of EGLN appears to be a stereospecific effect of the D-2HG enantiomer, as (L)-enantiomer of 2-hydroxyglutarate (L2HG) is reported to inhibit EGLN activity (57). In preclinical models, expression of IDH1-R132H in myeloid cells determined splenomegaly, but also reduces bone marrow cellularity, and the authors observed the abundance of hematopoietic progenitor cells in a manner that corresponds with increased histone H3 methylation and CpG island hypermethylation (58). These data are confirmed by the observation that patient AML cells with IDH1 or IDH2 mutations show a common hypermethylated DNA phenotype and that transgenic expression of IDH2R140Q or IDH2R172K injurie the differentiation of 32D cells (a murine myeloid progenitor line) in cell culture (39). Collectively, evidence from AML patients and preclinical models strongly suggests that IDH1 and IDH2 mutations represent oncogenic drivers of AML and myelodysplastic syndrome (MDS) and that targeting IDH mutant neomorphic activity in this context may offer therapeutic benefit by promoting the differentiation of malignant myeloid cells (29,40). Like the results in hematopoietic model systems, expression of IDH1-R132H mutation in central nervous system (CNS) tissues has been highlighted to alter neurodevelopment and impair the differentiation of neural progenitor cells (59,60). Specifically, Sasaki *et al.* expressed IDH1-R132H under the control of the nestin or glial fibrillary acidic protein (GFAP) promoters in murine CNS cells and did not observe IDH1-R132H-dependent

Table 3 Mutant IDH1 and IDH2 inhibitors

Drug name	Target	Mechanism of action	Regulatory information-FDA	BBB penetration
Ivosidenib	IDH1 R132 C, H, G, S, L	Reversible, allosteric, competitive inhibitor	FDA approval for relapsed/refractory acute myeloid leukemia [2018] and for newly diagnosed [2019]. FDA approval for previously treated, locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation [2021]	Unknown, 4.1% of penetrance in a rat model
Enasidenib	IDH2 R140Q, R172K	Allosteric, non-competitive inhibitor	FDA approval for relapsed/refractory acute myeloid leukemia [2017]	No information
Vorasidenib	Pan inhibitor, IDH1/2	Allosteric, non-competitive inhibitor	FDA granted fast track designation to vorasidenib in IDH+ low-grade glioma [2023]	Penetrance in a rat model
AG 5198	IDH1 R132 C, H	Reversible, allosteric, competitive inhibitor to αKG	None	Penetrance in mouse glioma xenografts
BAY 1436032	IDH1 R132 C, H, G, S, L	Allosteric, non-competitive inhibitor	None	Penetrance (low): 0.06–0.38 brain to plasma ratio in a mouse model

IDH, isocitrate dehydrogenase; FDA, Food and Drug Administration; BBB, blood-brain barrier; αKG, α-ketoglutarate.

glioma formation (37). Instead, expression of mIDH1 resulted in perinatal lethality in all nestin and the majority (92%) of GFAP-promoter driven mIDH expression. The remaining percentage (about 8%) of GFAP-IDH1-R132H mice survived into adulthood and many of the surviving mice developed splenomegaly and liver tumors, likely due to leakiness of the GFAP promoter-regulated expression of Cre-recombinase in non-CNS tissues (39). A more recent study used a tamoxifen-inducible strategy to conditionally express IDH1-R132H in neural progenitor cells in 5–6 weeks old mice (61).

IDH-mutant inhibition

Given this biological reasoning, numerous research initiatives were conducted with the aim to discover therapies targeting IDH and explore their potential as anti-cancer medications. Preliminary investigations have demonstrated the *in vitro* effectiveness of IDH inhibitors. It has been demonstrated that in IDHmutant (IDHmut) glioma, there is an increasing of oxidative stress caused by reduction of NADPH production in glioblastoma cell line with IDH1(R132H) mutation. This seems to explain the increased overall survival (OS) in these patients, because the IDH1mut cells have less ability to survive to oxidative stress induced by ionization radiotherapy. These results may explain the longer survival of patients with IDH1-mutated tumors and that IDH1 inhibitor should not be used during radiotherapy (62).

The first IDH1 inhibitor, AGI-5198, was used by Popovici-Muller and colleagues in 2018. This molecule demonstrated a significant reduction (up to 90%) in 2-HG levels in a U87 glioblastoma xenograft mouse model. Subsequently, Rohle *et al.* found that AG-5198 not only inhibited 2-DHG but also induced the expression of differentiation markers, decreased cell proliferation and histone methylation within the same cell line. Despite these promising results, the suboptimal pharmacodynamic characteristics of AGI-5198 (i.e., rapid metabolism and clearance), have hindered its progression into clinical trials (63,64).

This molecule was followed by a series of inhibitory IDHs capable of binding to an allosteric site, stabilising the mutant enzyme in an open and inactive conformation, blocking the conformational change required for catalysis. Examples are specific inhibitors of mIDH1 (ivosidenib or AG-120; BAY-1436032) and mIDH2 (enasidenib; AG-221) as well as a dual inhibitor of mIDH1 and mIDH2 used both (vorasidenib; AG-881) in AML (65,66) (*Table 3*).

Therefore, it is crucial to highlight the significance of IDH125, which possesses the ability to penetrate the blood-brain barrier (BBB), ensuring an optimal inhibition of D-2HG production. Additionally, IDH305 is a more soluble molecule with improved clearance kinetics and favourable inhibitory potency while IDH305, able to decrease the D-2HG production in IDH2 mutant cells to the same extent as IDH125, was tested in a clinical study (NCT02381886 trial). In this study patients with advanced-stage tumors carrying the IDH1 mutation were enrolled with promising early phase 1 safety results (67). DS-1001b,

is another inhibitor currently under investigation in clinical trials (NCT03030066 and NCT04458272) involving patients with IDH1-mutant gliomas. It exhibits excellent BBB permeability and significantly decreases D-2HG production caused by IDH1-R132H and IDH1-R132C mutations. However, it shows limited effectiveness against IDH1-R132G, IDH1-R132L, and IDH1-R132S, and it does not inhibit IDH2 variants (68).

There are currently several phase I/II studies for new IDH inhibitors, such as the NCT02719574 study, which is evaluating the efficacy of the specific IDH1 mutant olutasidenib in patients with acute myeloid leukemia or MDS. Additionally, there is ongoing research on innovative "second-generation inhibitors". Such as LY3410738 (NCT04521686 and NCT04603001) a molecule that not only forms a covalent bond with IDH but also robustly binds to IDH1 second-site mutations so conferring resistance to other inhibitors (69,70).

Crucially, it was observed by researchers that merely reducing D-2HG levels did not reliably indicate a clinical response. Many patients who did not respond to the therapy exhibited significant suppression of D-2HG. Instead, the researchers identified that mutations in genes associated with activating the RAS signalling pathway were more prevalent in non-responding patients (71) (refer to *Table 1*).

Resistance mechanisms

In spite of the optimistic findings outlined, there have been preliminary indications of acquired resistance mechanisms to these small inhibitors. This resistance leads to the advancement of the disease, accompanied by a rise in plasma 2-DHG concentration. Currently, ivosidenib and enasidenib have been approved for the treatment of IDH1- and IDH2-mutant AML, respectively. However, some patients harbouring IDH mutations show no response to monotherapy with mIDH inhibitors. Additionally, some patients experience relapse with increased circulating levels of 2-DHG and acquired resistance to IDH-targeted therapies. Among the initial instances of resistance, two patients with acute myeloid leukemia carrying the IDH2-R140Q mutation developed resistance to the IDH2 mutant inhibitor enasidenib. This resistance emerged following the occurrence of IDH2 second-site mutations, which can manifest in cis or trans (Q316E, I319M) in the wild-type allele. This collaboration with the gain-of-function mutation (R140Q) on the other allele induced resistance by disrupting the hydrogen bond between the IDH2 dimer and enasidenib or by hindering the binding of the IDH2 dimer to enasidenib. However, individually expressed, these second-site variants fail to generate D-2HG. Nonetheless, D-2HG production is restored upon co-expression with IDH2-R140Q, leading to the reinstatement of the self-renewal capacity of leukemic cells *in vitro* (72).

Mutations in the receptor tyrosine kinase (RTK) pathway may lead to primary resistance to ivosidenib (73). Conversely, the causes of acquired resistance can be multifactorial. In this context, the IDH1-R132C mutation was succeeded by an IDH1-S280F mutation, which is paralogous to residue I319 in IDH2. Other acquired second-site mutations in IDH1 include R199P, G131A, G289D, and H315D94. It is noteworthy that these mutations typically involve distinct subclones that emerge during treatment. In some cases, they may also be present at the treatment's onset, highlighting the parallel expansion of multiple subclones with branching patterns and linear clonal evolution (74).

This resistance mechanism arises from the emergence of mutations in the opposite IDH isoform, which would still respond to D-2HG even during treatment with an IDH inhibitor. Furthermore, 2-HG induces hypermethylated Wnt inhibitory signals, with increased stemness. It follows that 2-HG resulting from IDH mutations enhances leukemia stemness, hindering cellular differentiation and leading to primary resistance to IDH inhibitors (75).

In summary, the development of new mutations in the opposing IDH isoform leads to resistance against mIDH1 or mIDH2 inhibitors, resulting in elevated D-2HG levels. This mechanism is under investigation in a clinical study involving the dual IDH1 and IDH2 inhibitor vorasidenib (NCT02492737). This molecule seems to be effective in the presence of known IDH1 second-site mutations due to its unique binding mode. However, it is still unclear how this drug prevents isoform switching. Another study with LY3410738 is ongoing. This molecule could be active in the context of known IDH1 mutations in the second site due to its unique mode of binding, which prevents isoform switching (76). D-2HG-restorative IDH second-site mutations still need to be investigated, as increases in D-2HG levels have been observed in IDH-independent mutants. It appears that some tumors have a predilection for D-2HG (77). Therefore, to improve the effectiveness of mIDH inhibitors and overcome these resistances, various therapeutic strategies are being studied. An alternative involves the use of targeted short hairpin RNAs, revealing a synthetic lethal relationship between BCL2 and IDH

aberrations in AML cells. Enasidenib would reduce D-2HG levels, resulting in a reduction of cytochrome c oxidase activity. This process would lower the mitochondrial threshold for apoptosis activation following BCL-2 inhibition (78). Thus, in IDH-mutated hematological neoplasms, the association between the BCL-2 inhibitor venetoclax and ivosidenib (NCT03471260) is under study. In acute relapsed/refractory AML with IDH2 mutation (NCT04092179), a planned phase I/II was designed to investigate safety as well as effectiveness of enasidenib in combination with venetoclax (79).

In the phase III AGILE study (NCT03173248) and in other phase I/II studies, the combination of ivosidenib with hypomethylating agents such as azacitidine is under evaluation (80) (refer to *Table 1*).

IDH-mutant cholangiocarcinoma

Biliary tract cancers (BTCs) comprise a diverse group of aggressive malignancies that originate from various locations along the biliary tree, both inside and outside the liver. According to the updated anatomical classification, BTCs include iCCA, extrahepatic CCA (eCCA), which can be further categorized into perihilar (pCCA) and distal CCA (dCCA), as well as gallbladder cancer (GBC) and ampulla of Vater cancer (AVC) (81).

These tumors are often diagnosed at an advanced stage and typically do not respond well to chemotherapy, resulting in a grim outlook with a 5-year OS rate ranging from 7% to 20% (82). The underlying reasons for this aggressiveness have not been thoroughly explored. Currently, the only curative option for localized BTCs is surgical resection, but the recurrence rate remains high. Despite efforts to study the genomic characteristics of iCCA, there is still a lack of targeted therapies specifically designed for this subtype of liver cancer. It is crucial to gain a deeper understanding of the key driver events and evolutionary processes involved in ICC to develop more effective treatments (83). In recent years many studies have outlined a variety of molecular changes, including FGFR2, IDH1, HER2, MSI or BRAF, have the potential for targeted interventions.

The bile ductular and small duct subtypes of cholangiocarcinoma most commonly contain IDH1 mutations, specifically IDH1-R132C and IDH1-R132G, with a smaller percentage of cases having IDH2-R172 mutations. Missense mutation R132C is the most prevalent IDH1 mutation (44%) over the rest (84,85).

Numerous studies have evaluated the prognostic implications of these IDH mutations in cholangiocarcinoma, obtaining conflicting results regarding survival (86).

Several mouse models have investigated the effect of mIDH2 and demonstrated that IDH mutations alone do not generate hepatic or biliary lesions *in vivo*. However, the interaction of mIDH2 with the altered expression of transcription factors, oncogenes or tumor suppressors can generate tumor proliferation or aggressiveness *in vivo* (87). In 2014, Saha and colleagues conducted a study where they explored the control of the transcription factor SOX9, which is an early indicator of biliary cells within the liver. Their findings revealed that the regulation of SOX9 led to the downregulation of HNF4α, resulting in reduced differentiation of hepatocytes and an increase in cell proliferation in the liver (52).

In another *in vivo* experiment, which involved the introduction of IDH1-R132C, loss of p53 expression, and activation of Notch signaling within the liver, iCCA developed as early as 12 weeks after the injection of the Sleeping Beauty transposase expression vector. This model exhibited several characteristics associated with human iCCA, including the expression of CD19, the presence of collagen fibres, and active cell proliferation (88).

A potential drawback of previous experimental investigations into the roles of mIDH in the sustained growth of advanced solid malignancies is linked to the types of model systems employed. These models include xenografts, cell line or spheroid models, and engineered cancer models where ectopic mIDH1 expression doesn't contribute to tumor initiation. These models may not fully capture important biological aspects of natural tumors. For this reason, in Wu *et al.*'s 2022 study, genetically engineered mouse models (GEMM) were presented to examine the functions of mIDH1 in the development of iCCA. Using a GEMM in which mIDH1 significantly promotes ICC development and related allograft models, a crucial pathway controlled by (R)-2HG was identified that coordinates epigenetic reprogramming and immune evasion. Inhibition of this pathway improved responsiveness to immunotherapy (89).

Interestingly, it's worth noting that IDH1 mutations have been observed at a higher rate thus far, particularly in iCCAs that are not associated with hepatitis virus infection or *Opisthorchis viverrini* (90).

Just as they do in various other cancer types (several hematological and solid malignancies—such as glioma, iCCA, and acute myeloid leukemia), IDH mutations in cholangiocarcinoma disturb the typical differentiation

patterns of hepatocytes and result in abnormal hypermethylation profiles triggered by D-2HG (91-93).

In particular, hypermethylation determines, most of the time, a downregulation of TET2 function, suggesting a phenotypic overlap in the same way as what is observed between IDH and TET2 mutations in AML; this data emerges from an analysis integrating whole-genome, transcriptomic and epigenomic data of 489 cholangiocarcinomas conducted by Jusakul *et al.* (94). Another study conducted in 2013 found that there are 5,758 CpG sites associated with 2,309 hypermethylated genes in IDH-mutant cholangiocarcinomas and that half of these genes are also hypermethylated in IDH mutant glioblastomas. Furthermore, 16 hypermethylated genes are underexpressed in both tumor types (95).

The presence of these common traits, rooted in similar genetic foundations across various tumors, indicates the existence of a shared mechanism in disease development. This, in turn, suggests the possibility of overlapping therapeutic strategies. Over the past few years, a considerable range of IDH inhibitors has been examined for their efficacy in IDH mutant cancers. Among these, ivosidenib (AG-120), first approved for the treatment of AML, stands out as the most advanced IDH inhibitor for CCA. A phase I clinical trial involving 73 individuals with advanced IDH1 mutant CCA led to the choice of 500 mg as the recommended dose of ivosidenib monotherapy. Furthermore, patients reported only objective, partial responses (PRs) or stable disease with significant reduction in plasma D-2HG levels compared to baseline levels. Two patients experienced the emergence of IDH mutations (specifically, IDH1-R132F and IDH2-R172V) during treatment, leading to resistance against the therapy (96).

More recently the phase III ClarIDHy study (NCT02989857) eligible patients with chemotherapy-refractory IDH1 mutated cholangiocarcinoma (70% with the IDH1-R132C mutation) received ivosidenib (n=124) or placebo (n=61). The treatment revealed a favorable safety profile showing median progression-free survival (mPFS) 2.7 months compared to 1.4 months with placebo and hazard ratio (HR) 0.37, 95% confidence interval (CI): 0.25–0.54; P<0.0001 while median OS (mOS) was unchanged between the two groups (97).

Saha and colleagues carried out additional preclinical investigations involving 17 BTC cell lines, screening them with 122 Federal Drug Administration (FDA)-approved drugs. Notably, the multi-target IDH tyrosine kinase inhibitor dasatinib demonstrated remarkable efficacy and specificity in targeting iCCA cells that carried IDH mutations. Other drugs, such as BCL-2 inhibitors and nicotinamide phosphoribosyltransferase (NAMPT) inhibitors active against other IDH-mutant tumors, were ineffective. Rous sarcoma oncogene (SRC) was identified as the main target of dasatinib in IDH-mutated cholangiocarcinomas thanks to the use of "gatekeeper" mutations that confer resistance to the drug in each of the inhibited kinases. Another phase 2 clinical study (NC T02428855) investigated the effect of dasatinib on 8 patients with mIDH CCA showing fair mPFS (8.7 weeks) and mOS (37.9 weeks) (98).

NCT03684811 it is instead a multicenter, phase Ib/II, open-label clinical study, investigating the mIDH inhibitor olutasidenib (FT-2102), in patients with relapsed or progressing solid tumors with IDH1-mutated. Between primary and secondary outcome measures are present objective response rate (ORR) to olutasidenib and recommended doses, PFS, time to progression, duration of response, OS, cerebrospinal drug level fluid and time to reach peak plasma concentration (99).

DNA damage response (DDR) alterations have also been described in CCA IDH-mutated due to their effect on aKG dioxygenases. Indeed, preclinical models have suggested the sensitivity of IDH mutant CCA cells towards PARP inhibitor (PARPi) could be enhanced by high levels of 2-HG. Therefore, studies of monotherapy with olaparib (NCT03212274) and of association olaparib (PARPi) with durvalumab (NCT03991832) were initiated.

Another phase 2 study is combining olaparib with ceralasertib (ATR inhibitor) in mIDH solid tumors (NCT038780950). However, the results obtained so far are not brilliant (100).

Moreover, the exploration of combining IDH inhibitors with chemotherapy or systemic immunotherapy presents an additional avenue currently undergoing assessment (refer to *Table 1*). Specifically, there is an ongoing phase I study focused on dose reduction, investigating the combination of ivosidenib and CisGem as a primary treatment for patients with metastatic disease (NCT04088188). On the flip side, there is an ongoing phase II clinical trial assessing the concurrent use of nivolumab and ivosidenib in advanced solid tumors carrying IDH1 mutations, which includes CCA (NCT04056910) (101).

IDH mutation in LGG

IDH1 is the most frequently mutated gene in low-grade

gliomas (nearly 80% of cases), with the R132H mutation being the most frequently evidenced (102). Patients with grade 3 astrocytomas with IDHmut have a better prognosis than IDH wild type (IDHwt) astrocytomas (mOS 51 *vs.* 22 months) (102).

Moreover, IDH mutations provide the G-CIMP hypermethylated state and a proneural gene-expression profile (103,104). In this regard, although the immunosuppressive nature of gliomas has been well documented (105), the exact roles of mIDH and D-2HG production in immunosuppression remain unclear and under evaluation. Precisely, the overall amount of tumor-infiltrating lymphocytes is lower in IDH-mutant versus IDH-wild-type gliomas (105). Furthermore, subsequent analyses of particular immune cell subsets revealed the presence of a global reductions of microglia, macrophages, dendritic cells, B cells and T lymphocytes (106).

Additionally, it is well known that the selective permeability of the BBB represents a selective barrier to the delivery of systemic therapies in the CNS (107).

In this regard, the expression of ATP-binding cassette transporters in tumour cells often results in the efflux of drugs that do penetrate the BBB, that even further can prevent drug delivery.

These difficulties must be taken into account during drug development to achieve effective glioma targeting. In this regard, patients with glioma were included in a phase I multi-centric basket trial focused on the safety of ivosidenib used in patients with IDH1-mutant solid tumors (NCT02073994). In general, the molecule was well tolerated, with 13 (19.7%) of 66 patients with advanced-stage gliomas having grade ≥3 adverse events (AEs), and they observed only two AEs related to the treatment. Regarding efficacy results, among the 35 patients with non-enhancing lesions, the ORR was 2.9%, with one PR. In this group the authors achieved a stable disease in 85.7% of patients (30) compared with 45.2% (14) of those with enhancing gliomas. The authors achieved a mPFS of 13.6 months for patients with non-enhancing gliomas and 1.4 months for those with enhancing lesions.

Twenty-two of 33 patients experienced a reduced tumor volume and 9 (33.3%) of 27 evaluable patients with non-enhancing and enhancing lesions, respectively; patients with non-enhancing lesions, the authors demonstrated that the estimated tumor growth rate in 6 months decreased from 26% in the pre-treatment period to 9% with ivosidenib (108).

Recently, breakthrough results were achieved in this setting due to the use of another anti-IDH drug, vorasidenib. As a result, the phase III trial INDIGO may definitely change the therapeutic approach of low-grade astrocytomas. In this trial, patients with residual or recurrent grade 2 IDH-mutant glioma who had undergone no previous treatment other than surgery were randomly assigned patients to receive either an anti-IDH small molecule, oral vorasidenib or placebo. PFS was significantly improved in the vorasidenib group (mPFS 27.7 *vs.* 11.1 months) with a reduction of the risk of progression of 59% nearly. The time to the next intervention was significantly improved in the vorasidenib group (HR, 0.26; 95% CI: 0.15–0.43; P<0.001). AEs of grade 3 or higher occurred in 22.8% of the patients who received vorasidenib and in 13.5% of those who received placebo (109).

Hopefully, IDH-inhibitors will soon take part in clinical practice in neuro-oncology to completely change and improve life-expectancy of LGGs patients.

Discussion and future perspectives

As above mentioned, the biological importance of IDH alterations in cancer development is independent by the cell or cancer type and relies upon the overproduction of D-2HG and hypermethylation and blocks the normal differentiation patterns. In spite of these commonalities, the IDH-mutation activity differs in cancer subtypes on its role in metabolism and response to therapy, suggesting histologic-dependent, organ-dependent and even differentiation state-dependent phenotypes (110).

The knowledge of the biological effects of IDH mutation helps to find the correct setting amenable to reach the maximum efficacy after its inhibition.

First of all, the loss of wild-type or mIDH alleles leading to reduced D-2HG production during glioma progression, coupled with a greater efficacy to mIDH inhibitors in patients with non-enhancing gliomas, suggesting that targeting gliomas in their lower grade state, when most dependent on IDH mutations, must be considered for maximum therapeutic efficacy. As in the other oncological therapeutic strategies, the best first, and at an early stage (108,111).

Moreover, it is well known that immune response is downregulated in all IDH mutant cancer subtypes (112). Thus, IDH inhibitors could convert these immunologically cold tumors into immunologically hot tumors, improving the benefit of this therapeutic approach.

Lastly, we know that IDH mutations occur in the early stages of tumorigenesis, but several ongoing trials are enrolling patients with advanced-stage disease. Given that

the dependence on IDH mutant metabolites varies between cancers and with tumour evolution, the timing of IDH-targeted therapy and the inclusion of additional agents are imperative to increase the outcomes of patients with IDH-mutated cancers. Unfortunately, the molecular search of this alteration is not feasible in all oncological centres. Thus, in addition to the rarity of IDH mutation, the lack of its standardised analysis may provoke an underestimation of its incidence.

Conclusions

In conclusion, great advances have been achieved in understanding the biology of IDH mutations in a variety of cancers. On the contrary, the pathogenic roles of this molecular alteration are not well understood. Certainly, these hotspot mutations remain a promising therapeutic target; hopefully, will dramatically change the therapeutic approach in some "orphan" tumors.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-24-17/rc

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-24-17/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-24-17/coif). R.A. serves as an unpaid editorial board member of *Chinese Clinical Oncology* from August 2022 to July 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Internò V, Melaccio A, Vitale P, Spedaliere R, Buonfantino M, Messina R, Lippolis AL, Signorelli F, Addeo R, Giuliani F. Therapeutic inhibition of isocitrate dehydrogenase mutations in glioma and cholangiocarcinoma: new insights and promises—a narrative review. Chin Clin Oncol 2024. doi: 10.21037/cco-24-17