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IDH inhibitors in advanced cholangiocarcinoma: Another arrow in the quiver?

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ABSTRACT

Cholangiocarcinomas (CCAs) are a heterogenous group of hepatobiliary tumors with poor prognosis and limited therapeutic options. In the last decade, the advent of genomic profiling has led to the identification of several putative actionable aberrations in CCAs, and genomic characterization is playing an increasing role in the management of these malignancies. Thus, a wide number of targetable mutations are currently under investigation, and early studies on this approach in CCAs have been recently presented or published. Among these, isocitrate dehydrogenase (IDH) mutations have been reported in approximately 15–20% of intrahepatic cholangiocarcinoma (iCCA) patients, while these aberrations are considered to be less frequent in perihilar CCA (pCCA), distal CCA (dCCA), and gallbladder cancer. Of note, the recent findings of the ClarIDHy phase III trial add to mounting evidence showing the potential advantages of molecularly targeted therapies in CCA, on the basis of a benefit in previously treated IDH1-mutant patients receiving ivosidenib versus placebo. However, although the results of this trial showed a statistically significant improvement in progression-free survival and overall survival for IDH-mutant CCAs treated with ivosidenib, several questions regarding the real impact of IDH inhibitors in this setting remain open.

In this review, we will provide an overview on the biological rationale behind the use of IDH inhibitors in CCA patients and current clinical implications of these molecularly targeted agents. The recently published results of the ClarIDHy – as well as ongoing clinical trials in this setting – are highlighted and critically discussed.

Introduction

Cholangiocarcinomas (CCAs) include a group of aggressive epithelial malignancies of the biliary tree, encompassing intrahepatic cholangiocarcinoma (iCCA) and extrahepatic cholangiocarcinoma (eCCA) - which is further subdivided into perihilar cholangiocarcinoma (pCCA) and distal cholangiocarcinoma (dCCA) [1-17]. Ten years after the publication of the landmark ABC-02 trial, the combination of cisplatin plus gemcitabine (CisGem) remains the current standard of care for patients with metastatic disease [18-22]. In 2010, this study showed the superiority of CisGem over gemcitabine monotherapy, with median overall survival (mOS) of 11.7 months and 8.1 months, respectively (Hazard Ratio [HR] 0.64; 95% Confidence Interval [CI] 0.52–0.80; $P<0.001$) [21]. However, the reference doublet has provided an overall modest survival benefit, with most patients presenting a median survival of less than a year from the moment of diagnosis of advanced disease [23, 24]. Thus, impressive efforts have been conducted in the last decade to "raise the bar", including the use of novel agents as well as by adding a third drug to the standard of care regimen, with an attempt to improve clinical outcomes in CCA patients [25-27].

In fact, recent years have seen important advances in understanding the tumor biology and the molecular landscape of CCA, where the advent of genomic sequencing has led to the identification of several key oncogenic drivers in specific CCA subgroups [28-37]. Among these alterations, isocitrate dehydrogenase (IDH) mutations have attracted growing attention, with several IDH inhibitors which have been assessed or are currently under investigation in phase I and II clinical trials on IDH-mutant CCAs [38-40].

In this review, we provide an overview of the current literature regarding the role of IDH mutations in CCA, especially focusing on the biological rationale behind this therapeutic strategy as well as on recently published and ongoing clinical trials.

We performed a research on Cochrane library, PubMed/Medline, and Scopus using the following keywords "biliary tract cancer" OR

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"cholangiocarcinoma" OR "intrahepatic cholangiocarcinoma" OR "extrahepatic cholangiocarcinoma" AND "IDH" OR "ivosidenib" OR "IDH1 mutations" OR "IDH2 mutations" OR "isocitrate dehydrogenase". We selected the most relevant and pertinent studies considering how the studies were conducted, their applicability, statistical analysis, number of patients enrolled, outcomes. For ongoing clinical trials, we searched in the Clinicaltrials.gov database for recruiting and active, not recruiting trials, using the following keywords: "biliary tract cancer" OR "cholangiocarcinoma" OR "intrahepatic cholangiocarcinoma" OR "extrahepatic cholangiocarcinoma" AND "IDH" OR "ivosidenib" OR "IDH1 mutations" OR "IDH2 mutations".

Targeted therapies in cholangiocarcinoma: an evolving landscape

In the last decade, several studies have explored the molecular landscape of CCA, leading to the development of molecularly targeted treatments in this setting [41, 42]. However, novel treatment targets have been mainly assessed in iCCA patients, where the most promising genetic aberrations are represented by Fibroblast Growth Factor Receptor 2 (FGFR2) gene fusions and IDH mutations [43-45]. Other potential targets include BRAF mutations, NTRK gene fusions, HER2 amplification or overexpression, and DNA damage repair aberrations [46-50]. In particular, according to genomic sequencing, distinct genetic aberrations have been suggested to "clustered" in specific anatomical subtypes, and thus, molecular profiles vary widely between pCCA, dCCA, and iCCA [51]. In fact, IDH and FGFR2 aberrations have been mainly observed in iCCA patients, while HER2 amplifications or mutations are more common in eCCA and gallbladder cancer [52]. Of note, a large cohort of CCA patients – approximately the 50%, regardless of the anatomic subtype – is expected to harbor potentially druggable alterations, something which has led to the incorporation of genomic profiling in routine clinical practice of CCA [53, 54].

Among molecularly targeted therapies, FGFR inhibitors have been extensively studied in CCA, as also witnessed by the recent Food and Drug Administration (FDA) approval of pemigatinib for previously treated, unresectable locally advanced or metastatic CCA with FGFR2 gene fusions or rearrangements [55]. In fact, the FIGHT-202 study assessed the role of pemigatinib in 107 CCAs harboring FGFR2 fusions, reporting an overall response rate (ORR) of 35.5%, with a median PFS of 6.9 months, and a median duration of response of 7.5 months [56]. Several other FGFR inhibitors have reported promising early results, including infigratinib, derazantinib, and futibatinib, and are currently under investigation in phase III clinical studies [57-59]. However, the emergence of secondary resistance represents a notable issue limiting the duration of response of FGFR inhibitors, and representing a key challenge in this setting, where circulating tumor DNA and liquid biopsies could play an important role [60]. In fact, in the near future longitudinal liquid biopsy has the potential to enter into clinical practice, in order to track the evolution of secondary resistance mutations determining treatment failure; moreover, this tool could also guide selection of adequate treatment, guiding clinicians in this setting. As previously stated, although IDH and FGFR inhibitors represent the most extensively developed study in this setting, multiple potentially actionable genetic aberrations have been observed in CCA [61-63]. However, in the current paper we will not discuss recent trials regarding other molecularly targeted treatments in CCA, a topic which is beyond the specific scope of this review.

IDH mutations and the role of 2-hydroxyglutarate

Recent studies on the human genome have led to the identification of five IDH genes, which code for three different IDH enzymes [64]. IDH plays an important role in the Krebs cycles. In fact, IDH enzymes base their activity on the interaction with NADP (IDH1 and IDH2) and NAD (IDH3); IDH1 and IDH2 share several characteristics, since these two enzymes have a sequence similarity of 70% [65, 66]. In terms of function, in physiological conditions normal IDH1 and IDH2 enzymes are involved in a two-step reaction [67]; firstly, isocitrate is converted through oxidation to an intermediate compound – oxalosuccinate – resulting in the reduction of $NADP^+$ to NADPH. Subsequently, the beta-carbonyl group is released as CO_2 from oxalosuccinate, leading to the formation of α-ketoglutarate (α-KG) [68]. During the process of conversion of isocitrate to oxalosuccinate, the two H^+ atoms are "used" for the reduction of $NADP^+$ to NADPH and the conversion of the intermediate compound to α-KG [69] (Fig. 1).

On the basis of these premises, given the involvement of IDH1 and IDH2 in cell metabolism, gain-of-function mutations of these genes hesitate in the accumulation on 2-hydroxyglutarate (2-HG), with the neomorphic ability to convert α-KG into 2-HG [70]. Of note, this oncometabolite has been suggested to block the physiological cell differentiation, thus promoting tumorigenesis [71].

As regards CCA, IDH1 and IDH2 gene mutations have been reported in a range between 15 and 20% of iCCA patients, with the most commonly observed point mutations involving the R132 and the R172 codons [72]. In particular, IDH1 mutations are more frequent than IDH2 mutations, with the common involvement of the arginine 132 residue; more specifically, IDH1-R132C and IDH1-R132G represent the most commonly detected IDH mutations [72]. Notably enough, higher frequency of IDH1 mutations has been detected so far, appearing to be more common in iCCAs without hepatitis virus infection and non-Opistorchis Viverrini related [73]. Additionally, IDH1 mutations have been suggested to clustered with lower ARID1A expression while in rare, and even anectodal cases, with FGFR2 gene fusions [74]. Another interesting element is that IDH mutations have been associated with hypermethylated phenotypes, as noticed in several hematological and solid malignancies – such as glioma, iCCA, and acute myeloid leukemia [75-77]. Lastly, in terms of the prognostic value of IDH mutations in CCA, conflicting results have been reported so far [78].

The ClarIDHy trial: open questions and perspectives

In recent years, a wide number of IDH inhibitors has been assessed in IDH mutant malignancies. Among these, ivosidenib (AG-120) certainly represents the most "developed" IDH inhibitor in CCA. This molecule, which has been previously approved for the treatment of patients with IDH1 mutant acute myeloid leukemia, was firstly evaluated in a phase I clinical trial including 73 IDH1 mutant CCAs [79]. According to the results of this study, maximum tolerated dose (MTD) was not reached, with no dose-limiting toxicities; as regards the expansion cohort, the study has led to the selection of 500 mg as recommended dose. In terms of drug-related adverse events, treatment with ivosidenib was associated with grade 3 or more toxicities in the 5% of included patients; the most frequently observed adverse events included all grade fatigue, nausea, diarrhea, abdominal pain, decreased appetite, and vomiting, which were highlighted in the 42%, the 34%, the 32%, the 27%, the 27%, and the 23% of included patients, respectively. As regards clinical outcomes - and taking into account the inclusion of a highly pretreated patient population, median PFS was 3.8 months (95% CI 3.6–7.3), with 5% of participants achieving partial response (PR).

Abou-Alfa and colleagues recently published the results of the ClarIDHy trial [80]. In this randomized phase 3 study, previously treated IDH1-mutant CCA patients whose disease progressed following one to two systemic treatments were randomized to receive single-agent ivosidenib (500 mg once daily) or placebo [80]. Notably enough, the study design of the ClarIDHy allowed crossover to ivosidenib in patients receiving placebo at the time of documented radiographic progression. At the time of the data cut-off, 185 IDH1-mutant CCAs were randomized, with 124 and 61 patients in the experimental and the control arm, respectively [80]. PFS - primary endpoint of the study - observed a statistically significant improvement among ivosidenib patients compared with CCAs randomized to placebo (HR 0.37; 95% CI

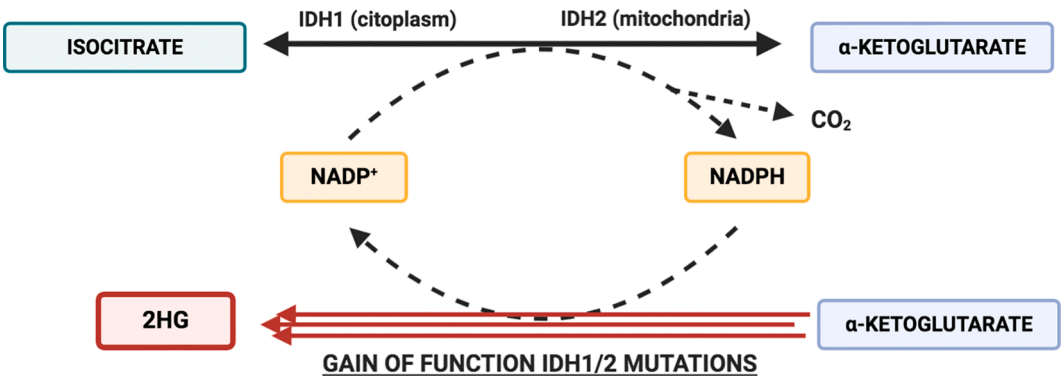

Fig. 1. Schematic figure reporting the impact of IDH1 and IDH2 mutations on the pathological accumulation of 2-hydroxygluatrate (2-HG). Isocitrate dehydrogenase (IDH)1 and IDH2 are located in the cytoplasm and mitochondria, respectively. Due to their role in cell metabolism and the process of decarboxylation of isocitrate to α-ketoglutarate, IDH1 or IDH2 mutations result in the pathogenic accumulation of 2-HG, an oncometabolite which promotes carcinogenesis. More details are reported in the text. *Abbreviations: IDH: isocitrate dehydrogenase; CO2: Carbon dioxide; $NADP^+$: nicotinamide adenine dinucleotide phosphate; NADPH: reduced form of NADP.*

0.25–0.54, $P<0.0001$), on the basis of a median PFS of 2.7 months in the experimental arm versus 1.4 months in the placebo group. Notably enough, the estimated PFS rate at 6 months and 12 months in patients treated with the IDH1 inhibitor were 32% and 22%, respectively; conversely, all IDH-mutant CCAs experienced disease progression before 6 months in the placebo arm. Stable disease (SD) was detected in the 51% and the 28% of the experimental and the control arm, respectivelyIn terms of toxicities, serious adverse events were reported in the 30% (36/121) and the 22% (13/59) of patients receiving ivosidenib and placebo, respectively. In particular, ascites was the most commonly detected grade 3 or worse adverse event in both treatment groups (7%); no grade 5 adverse events were reported in the trial.

Despite these promising results, some questions remain open and the ClarIDHy trial would deserve further discussion [81]. In fact, the use of placebo in a patient population with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1 with pretreated CCA could have produced an important bias, especially considering that – following the recently presented results of the ABC-06 phase III trial, cytotoxic chemotherapy with modified FOLFOX (mFOLFOX) should be considered as standard of care second-line treatment in advanced CCA. Thus, the inclusion of a control group with no active treatment could have affected the results of the ClarIDHy. In addition, although the statistically significant benefit of ivosidenib is undeniable, further efforts are needed to detect if this improvement could be translated into a clinically significant benefit. Notably enough, an advantage of 1.3 months in terms of PFS seems of limited value; for example, it would be interesting to assess if the IDH inhibitor could be superior to cytotoxic chemotherapy, and not simply placebo. Zhu and colleagues recently presented the final results from ClarIDHy, showing that ivosidenib improved OS by almost 3 months compared with placebo in pretreated patients. According to the results of the final analysis, mOS was 10.3 months for patients in the ivosidenib arm and 7.5 months for those in the placebo group (HR, 0.79), showing a numerical but not statistically significant benefit ($P = 0.93$) [82]. However, due to crossover, the authors used the prespecified rank-preserving structural failure time (RPFST) model to adjust OS; in this specific analysis, adjusted mOS was 5.1 months for CCA patients receiving placebo. Thus, this element made the OS benefit of ivosidenib significant, with a HR of 0.49 and $P<0.0001$. In addition, the 1-year OS rate was 43% with ivosidenib treatment and 36% with placebo.

Lastly, another important topic which could be borne in mind is cost-effectiveness. In fact, cost-effectiveness analyses should be a primary need in this setting, especially considering the balance between the magnitude of clinical benefit and the cost of ivosidenib – something which could limit the access to this treatment in several countries.

Other IDH inhibitors and ongoing clinical trials in cholangiocarcinoma

Apart from ivosidenib, the role of other IDH1 and IDH2 inhibitors is currently under evaluation in several phase I and II clinical trials (Table 1). Among these agents, preclinical studies have previously highlighted the activity of the IDH inhibitor dasatinib against iCCA cells harboring IDH mutations [83]; moreover, since this tyrosine kinase inhibitor targets SRC - and given the close association between SRC activity and iCCA cells proliferation and survival, these findings supported the exploration of this agent in this setting. In fact, a phase II trial has tried to translate this evidence into a clinical study on iCCA patients (NCT02428855). Although the recruitment for this trial has been completed, results are still awaited.

Another agent, olutasidenib (FT-2102), is being assessed a phase I/II trial on advanced solid tumors with IDH1 mutations – including iCCAs (NCT03684811). According to the study design of this trial, dose determination will be firstly assessed in IDH-mutant iCCA patients; subsequently, enrolled patients will receive the experimental treatment (olutasidenib) or the reference doublet CisGem. The study has a planned enrollment of 200 participants, with an estimated study completion date in April 2022.

An interesting area of current and future research involves the combination of PARP inhibitors (PARPi) with IDH targeting agents [84, 85]. In fact, preclinical models have suggested the sensitivity of IDH-mutant CCA cells to PARPi could be enhanced by high levels of 2-HG [86, 87]; in particular, several reports have observed concomitant alterations in the homologous recombination pathway and an increased PARPi sensitivity in IDH1-mutant tumors. Based on these premises, an ongoing phase II clinical trial is investigating the antitumor activity of the PARPi olaparib combined with ceralasertib (NCT03878095) in IDH-mutant solid tumors, including iCCA. The primary outcome of this study is ORR, with PFS, OS, duration of response, and incidence of adverse events which are also assessed as secondary endpoints. The trial has a planned enrollment of 50 participants, with an estimated study completion date in March 2023.

Lastly, the option of combining systemic chemotherapy or immunotherapy with IDH inhibitors represents another therapeutic option under evaluation (Table 1). In fact, a dose de-escalation phase I trial is exploring the combination of ivosidenib plus CisGem as first-line treatment in patients with metastatic disease (NCT04088188). The estimated enrollment of this trial involves 40 patients, and the study has an estimated completion date in September 2025. Conversely, a phase I trial is evaluating the combination of nivolumab plus ivosidenib in advanced solid tumors harboring IDH1 mutations, including CCA (NCT04056910). The study has a planned enrollment of 35 subjects.

Table 1
Ongoing trials evaluating isocitrate dehydrogenase (IDH) inhibitors as monotherapy or in combination with other anticancer agents (including PARP inhibitors, systemic chemotherapy, and immune checkpoint inhibitors) in advanced cholangiocarcinoma. *Abbreviations: CCA: cholangiocarcinoma; CisGem: cisplatin plus gemcitabine combination; DLTs: dose-limiting toxicities; iCCA: intrahepatic cholangiocarcinoma; IDH: isocitrate dehydrogenase; ORR: overall response rate; PFS: progression-free survival; RP2D: recommended phase 2 dose.*

NCT name	Phase	Setting	Arm A	Arm B	Estimated enrolment	Primary outcomes
NCT02428855	2	Advanced IDH1/2 mutated iCCA	Dasatinib		8	ORR
NCT03684811	1b/2	Advanced IDH1 mutated iCCA	FT2102	CisGem	200	DLTs ORR Doses recommended for future studies
NCT02073994	1	Advanced IDH1 mutated solid tumors, including CCA	AG-120		170	Safety/tolerability MTD
NCT02746081	2	Advanced IDH1 R132 mutated solid tumors, including CCA	BAY 1,436,032		81	Safety/tolerability MTD RP2D
NCT04521686	1	Advanced IDH1 R132 mutated solid tumors, including CCA	LY3410738		180	RP2D
NCT02481154	1	Advanced IDH1/2 mutated solid tumors, including CCA	AG-881		95	Safety/tolerability MTD RP2D
NCT02381886	1	Advanced IDH1 R132 mutated solid tumors, including CCA	IDH305		166	DLTs
NCT02273739	1/2	Advanced IDH2 mutated iCCA	Enasidenib		21	Safety/tolerability MTD RP2D
NCT04088188	1	Advanced CCA	CisGem + ivosidenib	CisGem + pemigatinib	40	Safety/tolerability
NCT04056910	2	Advanced IDH1 mutated solid tumors, including CCA	Nivolumab + ivosidenib		35	DLT Best overall response PFS
NCT03878095	2	Advanced IDH1/2 mutated solid tumors, including CCA	Olaparib + ceralasertib		50	ORR

Conclusions

The recently published results of the ClarIDHy trial have provided evidence in favor of the IDH inhibitor ivosidenib as novel therapeutic option in IDH-mutant CCA [80]. However, although we are witnessing a new era in medical management of CCA, as witnessed by the emergence of a wide number of molecularly targeted agents, further efforts are needed in order to modify the natural history of CCA.

Financial & competing interests' disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Alessandro Rizzo: Conceptualization, Methodology, Software, Data curation, Writing – Original draft preparation, Writing – Reviewing and Editing. **Angela Dalia Ricci:** Methodology, Writing – Original draft preparation and Editing. **Giovanni Brandi:** Visualization, Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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