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REVIEW

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Efficacy and safety of IDH inhibitors in IDH-mutated cancers: a systematic review and meta-analysis of 4 randomized controlled trials

Zelin Cai[1†], Huiting Yang[1†], Zhuoran Yu[3], Jingyang Su[2], Jie Zhang[3], Zhifeng Ye[4], Keke Hu[4], Ting Huang[4*] and Heran Zhou[4*]

Abstract

Background Isocitrate dehydrogenase (IDH) inhibitors have shown great promise in the treatment of cancers with IDH mutations. There have been numerous clinical trials conducted on IDH inhibitors, and to evaluate their efficacy and safety, we aim to perform a meta-analysis.

Methods To gather data on the efficacy and safety of IDH inhibitors for IDH-mutated cancers, we systematically searched through databases including PubMed, EMBASE, and Cochrane Library. Using RevMan5.4, we performed a meta-analysis and calculated the odds ratio (OR) or weighted mean difference (WMD) with a 95% confidence interval (95%CI). The parameters considered were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), treatment-related adverse events (TRAEs), and TRAEs ≥ 3.

Results This meta-analysis included four studies, involving a total of 751 patients. According to the analysis, there was no significant difference in overall survival, treatment-related adverse events, and severe treatment-related adverse events between the experimental group (receiving IDH inhibitors) and the control group. However, the progression-free survival, objective response rate, and disease control rate in the experimental group were significantly higher than those in the control group.

Conclusion The overall efficacy of IDH inhibitors in treating cancers with IDH mutations is superior to that of conventional medical therapy, potentially providing more clinical benefits to patients. The incidence of adverse events was not significantly different from conventional medical therapy. Therefore, IDH inhibitors should be considered as the preferred choice for treating cancers with IDH mutations. However, further randomized controlled clinical trials are still required for verification.

†Zelin Cai and Huiting Yang contributed equally to this work and share first authorship.

*Correspondence:
Ting Huang
huangtin100@sohu.com
Heran Zhou
290829031@qq.com

Full list of author information is available at the end of the article

Keywords Isocitrate dehydrogenase, Safety, Efficacy, Inhibitor, Meta-analysis

Introduction

The isocitrate dehydrogenase (IDH) gene spike was initially discovered in certain types of brain tumors, such as astrocytoma, oligodendroglioma, and secondary glioblastoma [1, 2]. However, further research has revealed that this gene spike is also present in other types of cancers, including acute myeloid leukemia (AML), myelodysplastic syndrome, myeloproliferative tumors, cholangiocarcinoma [3–5], and even rare aciduria [6, 7]. This discovery has led to the development of therapeutic research focusing on cellular energy and metabolic disorders as key characteristics of cancer [8].

IDH is an essential enzyme involved in cellular respiration in the tricarboxylic acid cycle. Mutations in the IDH1 or IDH2 genes are commonly found in various cancers, such as glioma, AML, chondrosarcoma, and intrahepatic cholangiocarcinoma [9]. These mutations result in altered IDH1 and IDH2 proteins with a new function that converts α-ketoglutaric acid (α-KG) to 2-hydroxyglutaric acid (2-HG). The increased levels of 2-HG in cells competitively inhibit α-KG-dependent enzymes that play crucial roles in gene regulation and tissue homeostasis. The expression of mutant IDH also impairs cell differentiation and can collaborate with other oncogenes to promote tumor development [10].

To investigate the inhibition of mutant IDH expression, preclinical studies have been conducted using IDH inhibitors. These studies have shown that mutant IDH1/2 inhibitors can delay the growth of IDH-mutant glioma cells and induce cell differentiation in tumor cells treated in vitro. Additionally, treatment with IDH inhibitors can reduce intracellular 2-HG levels and reverse DNA and histone hypermethylation in cells harboring IDH mutations [11–13]. Based on these promising IDH mutation-targeted therapy has been proven, leading to further development of mutant IDH inhibitors for clinical use.

Prior to the development of IDH inhibitors, there was no specific treatment for IDH mutations, and the standard treatment for IDH-mutated cancers varies depending on the specific tumor type [14]. However, the emergence of IDH inhibitors has brought hope for targeted therapy in myeloid malignancies with IDH1/2 mutations. Numerous clinical studies and evaluations of IDH inhibitors are ongoing to explore their efficacy in different IDH-mutated cancers, including cholangiocarcinoma and low-grade glioma [15]. Some randomized controlled trials of IDH inhibitors in IDH-mutant cancers have already been published, but no meta-analysis of their efficacy and safety in cancers with IDH mutations has yet been conducted.

Therefore, the purpose of this study is to conduct a meta-analysis of all relevant randomized controlled trials (RCTs) published up until June 1, 2023. The goal is to provide high-quality evidence-based medical evidence that can contribute to the development of clinical treatments and guidelines for cancers with IDH mutations.

Methods

This study has successfully been registered in the International Prospective Register of Systematic Reviews (CRD42023434065), which is an internationally recognized database that documents ongoing systematic review protocols. As part of our research methodology, we have adhered to the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy

To conduct a comprehensive search for studies on the topic, we used three major databases, namely PubMed, EMBASE, and the Cochrane Library, starting from their inception up to June 1, 2024. Our search strategy involved the utilization of specific keywords such as "cancer," "isocitrate dehydrogenase," and "inhibitors," without any language restrictions. To ensure accuracy and relevance of the retrieved articles, we tailored the retrieval format according to the unique characteristics of each database. Detailed steps for the retrieval process of each database can be found in Supplementary 1, Supplementary 2, and Supplementary 3. Screening of the identified articles was performed independently by two review authors, who adhered to predefined criteria. Any discrepancies or disagreements in the screening process were resolved through consultation with a third author. Furthermore, we extended our search effort by examining systematic reviews and reference lists of the included articles, aiming to identify additional relevant studies that may have been missed during the initial search.

Inclusion and exclusion criteria

Inclusion criteria: (1) The study design was a randomized controlled trial (RCT), meaning that the researchers assigned participants randomly to either the experimental or control group; (2) Patients with cancer were eligible to participate in the study; (3) Patients in the experimental group were treated with IDH inhibitors, which are a specific type of medication; (4) Patients in the control group were treated with drugs chosen by their physician; (5) The study reported at least one of the following data: overall survival (OS), which is the length of time a patient survives from the start of treatment; progression-free

survival (PFS), which is the length of time a patient lives without the cancer worsening; objective response rate (ORR), which measures the percentage of patients who experience a specific tumor shrinkage; disease control rate (DCR), which measures the percentage of patients whose tumors either shrink or stop growing; treatment-related adverse events (TRAEs), which refer to any negative or unexpected effects experienced by the patients during treatment; and TRAEs≥3, indicating the occurrence of severe adverse reactions.

Exclusion criteria: Studies that were not randomized controlled trials, such as observational studies or non-controlled studies; animal experiments, as they do not directly involve human participants; reviews, case reports, conference abstracts, and replication studies, as they do not present original data from a specific trial; studies with incomplete data, where important information was missing or not reported; and studies on irrelevant topics that are not related to cancer treatment.

Data extraction

Once the selection of studies had been determined, two researchers worked independently to gather the necessary information for inclusion in the analysis. This included noting the name of the first author, the year of publication, the sample size of the study, the age and gender of the patients involved, the type of tumor being studied, any previous treatments the patients had undergone, the status of the affected organ, the Eastern Cooperative Oncology Group (ECOG) performance status, and the intervention methods used in the study. Baseline statistics were also collected, which encompassed overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and treatment-related adverse events (TRAEs). Specifically, TRAEs that were of grade 3 or higher were also taken into account.

Once the two researchers had completed the extraction process, a third researcher then checked their work and made any necessary corrections to ensure accuracy. It is worth noting that all relevant information was extracted solely from the main text of the studies and accompanying supplementary files. Any data that could not be extracted was not included in the analysis. If further details were needed, the corresponding author of the study was contacted for clarification.

Statistical processing

We utilized RevMan 5.4, a software tool specifically designed for meta-analysis, to conduct our analysis. We examined the reported odds ratio (OR) or the weighted mean difference (WMD) along with their corresponding 95% confidence intervals (CIs) using fixed effects or random effects models. The fixed effects model was employed when the literature heterogeneity, as indicated by an I2 value less than 50%, did not yield a statistically significant difference. Conversely, if I2 was equal to or greater than 50%, indicating substantial heterogeneity, the random effects model was utilized. The key outcome measures in our analysis encompassed OS, PFS, ORR, DCR, TRAEs, and TRAEs≥3. Statistical significance was considered present when the p-value was less than or equal to 0.05.

Literature bias risk assessment

The Cochrane Collaboration's tool for assessing the risk of bias was employed to thoroughly evaluate the quality of all the studies included in the analysis. The risk of bias was evaluated from 7 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each bias was assessed as low risk, unclear risk, and high risk. For each of these items, the risk of bias was categorized as low risk when the study adequately addressed the criteria, unclear risk when the information provided was insufficient to make a judgment, and high risk when there was a clear indication of bias. By evaluating each study against these criteria, a thorough assessment of the risk of bias was obtained, ensuring the reliability and validity of the results.

Results

Literature screening process

After conducting a thorough screening process, a total of 3823 articles were initially considered for inclusion in the study. However, after meticulous evaluation, certain articles were excluded due to various reasons including the presence of duplicate literature, incomplete data, review articles, conference summaries, and other types of literature that did not meet the specific criteria set for this research. After this rigorous exclusion process, only 4 relevant literatures remained and were deemed suitable for further analysis and inclusion in the study. The detailed process of screening and selection can be found in Fig. 1, which illustrates the specific steps taken to arrive at the final set of literature to be included in the research.

Basic features of literature

The four included studies that were referred to in the statement were considered to be of medium and high quality randomized controlled trials. These trials were conducted with a total number of 751 participants. The details regarding the specific baseline characteristics of these four studies can be found in Table 1.

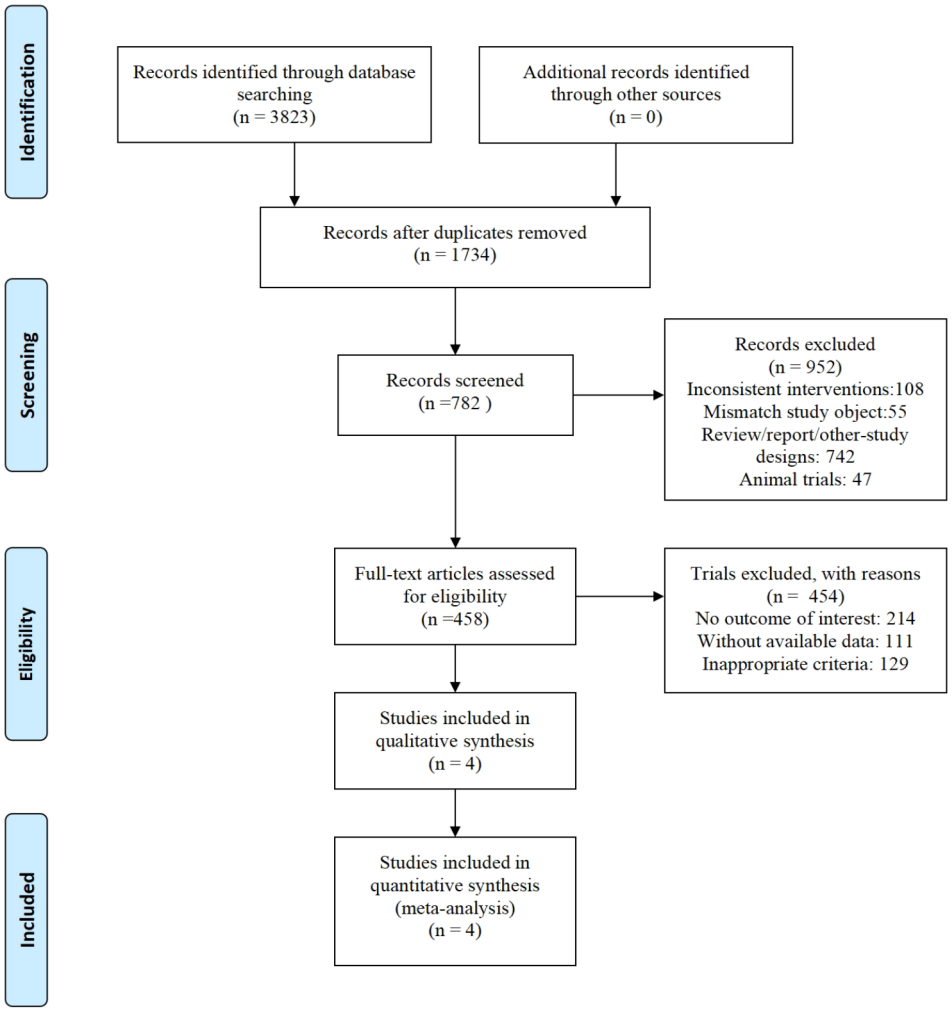

Fig. 1 Flow diagram for the selection of eligible studies

Literature bias risk assessment

According to the evaluation, all the four included literatures were medium and high quality randomized controlled studies. The detailed quality assessment is shown in Fig. 2.

Results of meta-analysis

Overall survival (OS)

All the 4 studies included in the analysis [16–19] provided data on the median OS of the participants. However, one of the studies [18] did not provide detailed information regarding the 95% CI of the median OS. Due to this lack of data, we decided to exclude this particular study from the analysis. When we assessed the heterogeneity between the included studies, we found that the I^2 value was above 50%. This indicated a significant level of heterogeneity among the studies. To account for this heterogeneity, we used a random effects model in our analysis. The result showed that there was no significant difference in OS between the experimental group and the control group [WMD=3.43, 95%CI -2.88, 9.74; P=0.29] (Fig. 3).

Progression-free survival (PFS)

Two articles [16, 17] all reported median PFS and 95% CI interval in detail, so all the articles were selected. The heterogeneity was small (I^2=0%), so the fixed effects model was selected. The results showed that the PFS of the experimental group was significantly higher than that of the control group [WMD=1.68, 95%CI 0.65, 2.71; P=0.001] (Fig. 4).

Objective response rate (ORR)

Three articles [16, 17, 19] reported ORR, so all the articles were selected. The heterogeneity was small (I^2=0%), so the fixed effects model was selected. The results showed that the ORR of the experimental group was significantly better than that of the control group [OR=5.72, 95%CI 3.58, 9.13; P<0.00001] (Fig. 5).

Table 1 Characteristics of studies and subjects included in the review

Study author (year)	Study design	Gender (M/F)	Case Experimental vs. control	Patients' characteristics	Intervention methods
Abou-Alfa 2020	RCT phase 3	68/117	185 124vs61	Patients from 49 hospitals in six countries aged at least 18 years with histologically confirmed, advanced, IDH1-mutant cholangiocarcinoma who had progressed on previous therapy, and had up to two previous treatment regimens for advanced disease, an Eastern Cooperative Oncology Group performance status score of 0 or 1, and a measurable lesion as defined by Response Evaluation Criteria in Solid Tumors version 1.1.	Oral ivosidenib 500 mg once daily vs. or matched placebo
Botton 2023	RCT phase 3	181/132	319 158vs161	Patients aged ≥ 60 years with de novo or secondary AML (World Health Organization classification20), a confirmed IDH2 gene mutation, and an Eastern Cooperative Oncology Group performance status score ≤ 2. At screening, patients were to have received 2 or 3 prior AML-directed therapies; prior hypomethylating agent (HMA) therapy for higher-risk myelodysplastic syndromes (MDS) also constituted an eligible prior therapy if the patient experienced progression to AML during or within 60 days after receiving the HMA.	Enasidenib 100 mg per day vs. conventional care regimen (CCR)
Di-Nardo 2021	RCT phase 2	/	101 68vs33	Eligible patients were aged 18 years or older and had newly diagnosed, mutant-IDH2 acute myeloid leukaemia, and an Eastern Cooperative Oncology Group performance status of 0–2	Enasidenib plus azacitidine vs. azacitidine only
Montesinos 2022	RCT phase 3	80/66	146 72vs74	Age of 18 years or older and a centrally confirmed diagnosis of previously untreated IDH1-mutated acute myeloid leukemia determined with the Food and Drug Administration–approved Abbott RealTime IDH1 in vitro polymerase-chain-reaction (PCR) assay. Additional eligibility criteria included no previous treatment with an IDH1 inhibitor or hypomethylating agent for myelodysplastic syndrome, an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 to 2 (on a 5-point scale in which higher scores indicate greater disability), and adequate hepatic and renal function.	Oral ivosidenib (500 mg once daily) and subcutaneous or intravenous azacitidine (75 mg per square meter of body-surface area for 7 days in 28-day cycles) or to receive matched placebo and azacitidine

Disease control rate (DCR)

Three articles [16, 17, 19] reported DCR, so all the articles were selected. The heterogeneity was large (I^2=62%), so the random effects model was selected. The results showed that the DCR of the experimental group was significantly better than that of the control group [OR=2.56, 95%CI 1.47, 4.46; *P*=0.0009] (Fig. 6).

Treatment-related adverse events (TRAEs)

The results showed that the TRAEs (OR=3.26, 95%CI 0.67, 15.95; *P*=0.15) and TRAEs≥3 (OR=1.46, 95%CI 0.79, 2.70; *P*=0.23) were no significant difference between the experimental group and the control group (Figs. 7 and 8).

Discussion

This study is the first meta-analysis to comprehensively evaluate the effectiveness and safety of IDH inhibitors as a treatment option for cancer. We included a total of four RCTs involving 751 patients with IDH-mutated cancers.

The results of our meta-analysis revealed significant improvements in PFS, ORR, and DCR in the experimental group compared to the control group. However, there was no significant difference in OS and TRAEs between the two groups. The lack of difference in OS outcomes suggests that IDH inhibitors may not confer a survival advantage over other treatment options. However, it is important to note that IDH inhibitors demonstrated remarkable benefits in terms of PFS, ORR, and DCR when compared to alternative therapies.

In terms of safety, over half of the patients receiving IDH inhibitors reported treatment-related adverse events grade 3 or higher (TRAEs≥3), although the incidence was lower than that in the usual care group. Nonetheless, the odds ratios for TRAEs and TRAEs≥3 were not significantly different between the IDH inhibitors group and the conventional treatment group. This suggests that while IDH inhibitors may be associated with a higher incidence of adverse events, the severity of these events is comparable to conventional treatments. Among the most common treatment-related adverse events reported across the included studies, nausea had the highest combined incidence of 30% (105/349) in patients receiving IDH inhibitors. Other common adverse events included increased serum bilirubin, thrombocytopenia, loss of appetite, vomiting, and diarrhea. However, it is important to note that these adverse events can be managed through dose adjustments or discontinuation of IDH inhibitors, glucocorticoid treatment, and supportive care. To ensure early detection and management of adverse

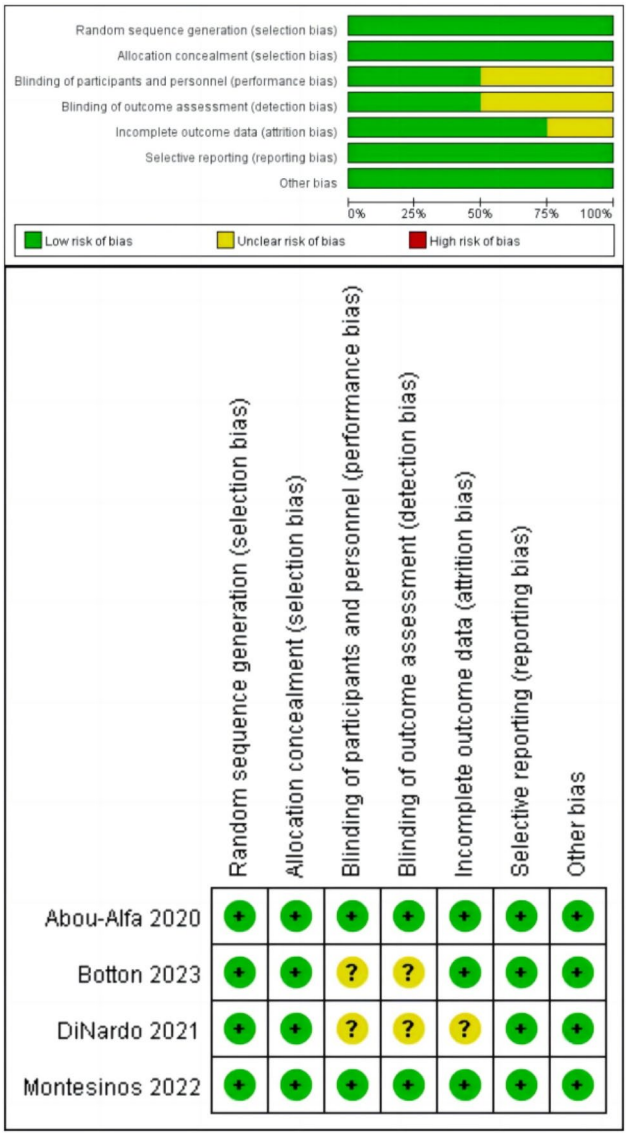

Fig. 2 Quality assessment of the included studies. (**A**) Summary of bias risk. (**B**) Risk of bias for each included study. "+" represents low risk of bias; "–" represents high risk of bias; and "?" represents unclear risk of bias

events, active monitoring and assessment of patients' signs and symptoms are crucial. Helpful assessments to consider include high-resolution computed tomography scans, consultations with appropriate specialists, oxygen saturation testing, and any other necessary diagnostic procedures.

While this study aimed to comprehensive evaluation of the effectiveness and safety of IDH inhibitors as a treatment option for cancer patients, it does have some limitations. Firstly, the small number of included articles limited our ability to conduct further subgroup analyses. Secondly, the limited number of patients in the four included studies may affect the reliability of the outcomes. Lastly, the high heterogeneity observed in the analysis results, even with the use of a random effects model, raises concerns about its potential impact on the findings.

In addition, I noticed that when I refer to literature, IDH research is now a lot of practice. For example, in the phase I study using ivosidenib, the researchers observed that patients in the enhanced disease cohort, who had gadolinium contrast material present on their MRI scans, had a longer duration of treatment and better progression-free survival compared to the nonenhanced group. Additionally, a significant proportion of patients in the nonenhanced group achieved remission. It was also noted that after treatment with ivosidenib, there was a decrease in the estimated tumor growth rate in patients with nonenhancing disease [20]. In regards to the role of IDH inhibitors in glioma treatment, there is still ongoing research to fully understand their effectiveness. Results from the ivosidenib study showed that patients treated with this inhibitor experienced prolonged stable disease and a reduction in the growth of non-enhancing tumors. On the other hand, vorasidenib demonstrated an overall response rate of 18% specifically in non-enhancing gliomas.In another recent study, called a phase 1b/2 study, olutasidenib, a selective mutant isocitrate dehydrogenase (mIDH) 1 inhibitor, was tested on 26 patients with recurrent mIDH1 gliomas, which mainly consisted of enhancing tumors. The study reported that the inhibitor was well-tolerated by patients and showed some promising early clinical activity in a group of patients who had received extensive prior treatment. Furthermore, there are ongoing clinical investigations exploring the potential of other mIDH inhibitors such as BAY1436032, DS-1001, LY3410738, and many more. These studies aim to further

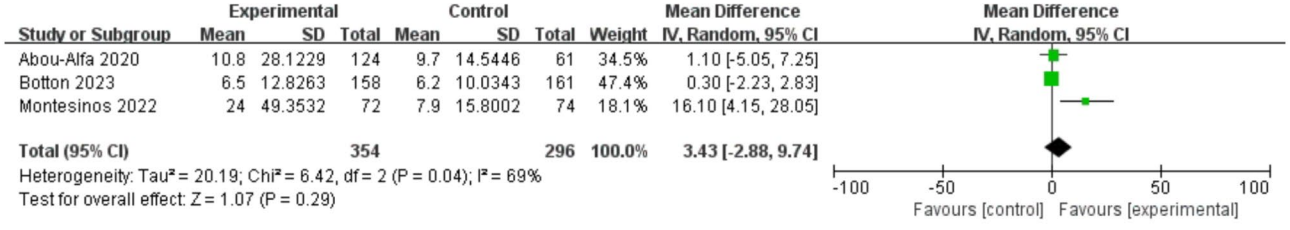

Fig. 3 Meta-analysis of the overall survival (OS) of IDH inhibitors in IDH-mutated cancers

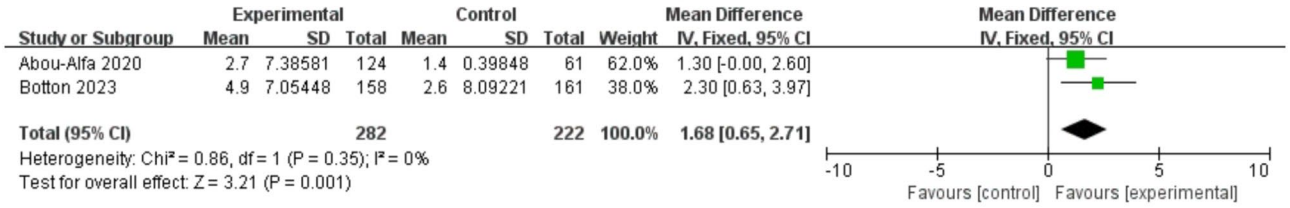

Fig. 4 Meta-analysis of the progression-free survival (PFS) of IDH inhibitors in IDH-mutated cancers

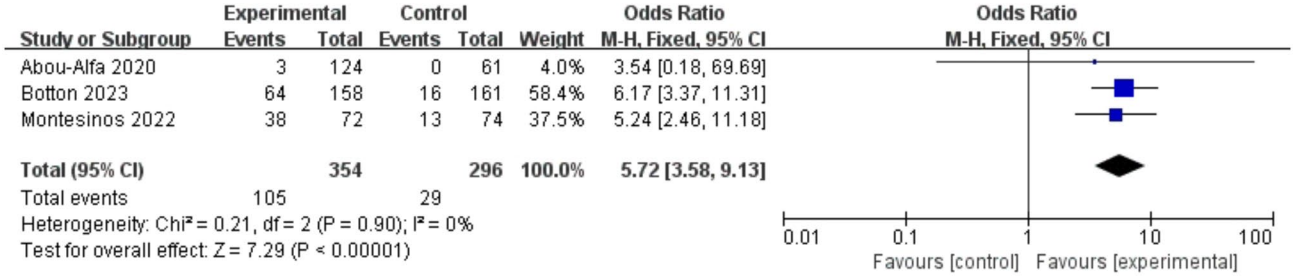

Fig. 5 Meta-analysis of the objective response rate (ORR) of IDH inhibitors in IDH-mutated cancers

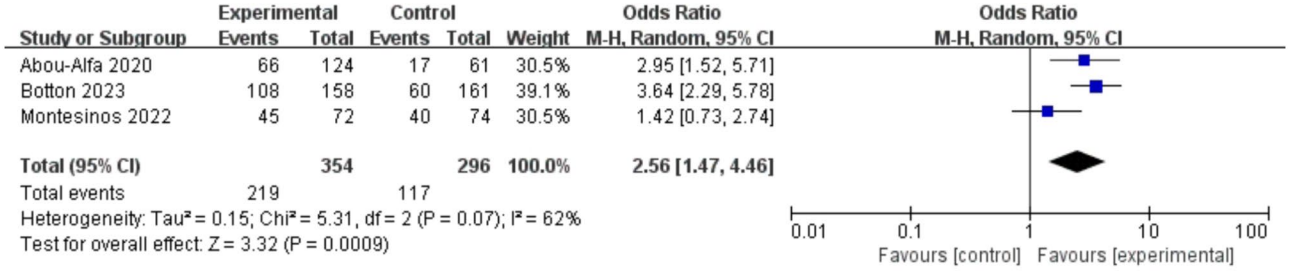

Fig. 6 Meta-analysis of the disease control rate (DCR) of IDH inhibitors in IDH-mutated cancers

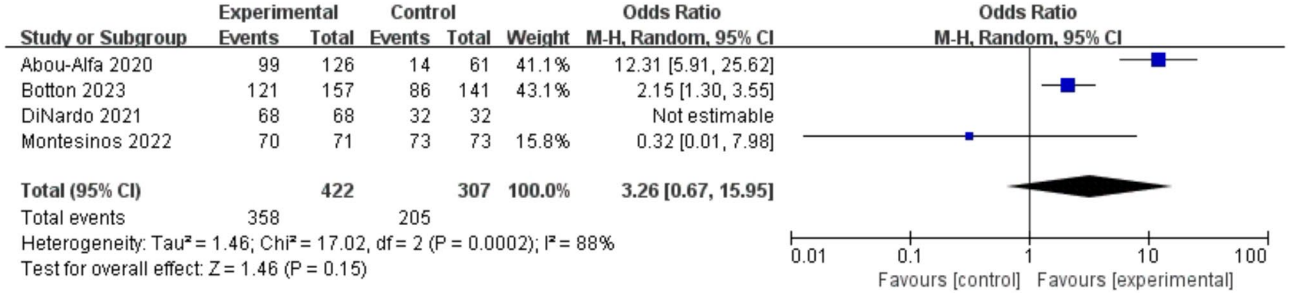

Fig. 7 Meta-analysis of the treatment-related adverse events (TRAEs) of IDH inhibitors in IDH-mutated cancers

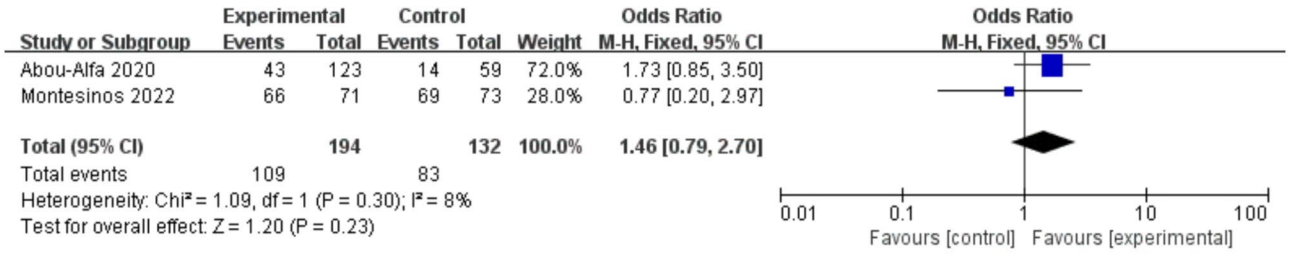

Fig. 8 Meta-analysis of the TRAEs ≥ 3 of IDH inhibitors in IDH-mutated cancers

expand our understanding of IDH inhibitors and their potential role in the treatment of gliomas [21, 22].

Several groups have identified and characterized mutations in the IDH gene in intrahepatic cholangiocarcinoma (iCCA). These mutations occur more frequently in IDH1 than IDH2, and they are known as "hotspot" mutations because they occur at specific points in the gene, specifically the arginine 132 (R132) residue in IDH1 and the arginine 172 (R172) residue in IDH2. These mutations are found at higher rates in iCCA compared to extrahepatic cholangiocarcinoma (CCA) cases. The mutant IDH protein loses its normal enzymatic activity and gains a new ability to produce a metabolite called 2-hydroxyglutarate (2-HG). This oncometabolite can be detected in both the tumor tissue and the bloodstream. Researchers have developed pharmacologic inhibitors that specifically target the mutant forms of IDH, such as IDH1-R132 and IDH2-R172. These inhibitors can effectively block the function of the mutant IDH enzymes at very low concentrations, resulting in a decrease in 2-HG levels. In laboratory studies, IDH inhibitors have shown the ability to inhibit tumor growth in cell lines harboring specific IDH mutations. One such inhibitor, AG-120 (ivosidenib), is a potent oral drug that targets mutant IDH1.

In addition to ivosidenib, other IDH1 and IDH2 inhibitors are currently being evaluated in clinical trials enrolling patients with CCA. These trials aim to further explore the potential of IDH inhibitors as a targeted therapy for this type of cancer. However, it is important to conduct further research in a larger study population to fully understand the effectiveness and safety of these inhibitors.

It is widely believed that the development of AML caused by IDH mutation may be associated with widespread hypermethylation of the entire genome. Consequently, the clinical treatment of AML typically involves the use of chemotherapy, targeted therapy, and hematopoietic stem cell transplantation. Extensive research has revealed that a considerable percentage (ranging from 38 to 86%) of chondrosarcoma cases involve IDH mutations. Furthermore, investigations have demonstrated the high frequency of IDH1 gene mutations (ranging from 60 to 80%) in oligodendroglioma, astroglioma, and secondary glioblastoma. Surprisingly, these mutations are almost entirely absent in primary glioblastoma tumors. Therefore, IDH inhibitors are highly likely to be used in the study of these lesions.

In addition, many new IDH inhibitors are currently under investigation. In 2015, Novartis announced the development of a new compound called IDH305, which is an oral inhibitor currently undergoing Phase I clinical trials. The drug has shown promising results, with an IC50 of 18 nM, indicating its potency in inhibiting the target enzyme. What makes IDH305 particularly impressive is its nearly 200-fold selectivity for mIDH1 R132H mutation over the wild-type IDH1. This selectivity ensures that the drug specifically targets cancer cells with the mutated enzyme while minimizing potential side effects on healthy cells. Prior to the clinical trials, preclinical tests were conducted to evaluate IDH305's efficacy. These tests demonstrated that the drug effectively reduces the level of 2-HG, a metabolite associated with tumor growth, in tumors. These positive results, combined with the compound's favorable pharmacokinetic properties, prompted researchers to move forward with the first clinical trial in 2016, registered under the identification code NCT02381886. However, despite the initial clinical trial, there have been no new updates or findings regarding IDH305 in recent years. It is unclear whether the lack of new research data is due to ongoing trials that have not yet released results or if the development of this specific compound has been halted.

In contrast to Novartis' IDH305, Agios Pharmaceuticals has developed a dual inhibitor called AG-881, targeting both IDH1 and IDH2 mutations. This drug has demonstrated effectiveness against various mutations, including IDH1 R132C, IDH1 R132L, IDH1 R132H, and IDH1 R132S, with IC50 values ranging from 0.04 to 22 nM. Currently, AG-881 is undergoing a Phase 1 trial for solid tumors, including gliomas, with encouraging outcomes for 93 patients. Additionally, clinical trials focusing on advanced hematological malignancies are also underway, indicating AG-881's potential in treating a broader range of cancers.

Similarly, Bayer has developed a highly selective and potent mIDH1 inhibitor called BAY1436032. This compound shows great promise in the treatment of AML [NCT03127735] and advanced solid tumors [NCT024746081]. However, there is a lack of available clinical reports or updates regarding the outcomes of these trials, leaving the current status and efficacy of BAY1436032 uncertain.

GSK321, another promising mIDH1 inhibitor, has shown high potency in preclinical studies. This compound has the ability to induce myeloid differentiation in IDH1 mutant cells, helping to restore normal cellular function. However, GSK321 is still in the preclinical stage and has yet to enter clinical trials.

Finally, Daiichi Sankyo has reported the development of a mIDH1 inhibitor called DS-1001b, specifically intended for the treatment of chondrosarcoma. Currently, DS-1001b is being studied in clinical trials to assess its effectiveness in treating recurrent or progressive gliomas [NCT03030066]. The results of these trials will shed light on whether DS-1001b can be a viable treatment option for these types of cancers.

Conclusion

IDH inhibitors are drugs that specifically target and suppress the expression of mutant IDH proteins, which play a crucial role in the development and progression of certain types of tumors. By inhibiting mutant IDH expression, these inhibitors effectively impede the growth and proliferation of cancer cells. Compared to conventional drug therapy approaches, IDH inhibitors have been demonstrated to be more effective in inhibiting tumor development in preclinical and clinical studies. This superiority stems from their ability to directly target the underlying genetic aberration that drives cancer growth, resulting in higher response rates and better disease control. Moreover, the incidence of adverse events associated with IDH inhibitors was found to be comparable to that of conventional medical therapy. This means that although these inhibitors offer improved efficacy, they do not significantly increase the risk of undesirable side effects for patients, making them a safe and viable treatment option.

Given their superior efficacy and comparable safety profile, IDH inhibitors should be considered as the first-choice therapy for IDH-mutated cancers. Based on the current available evidence, IDH inhibitors show great promise as a targeted therapy for IDH-mutated cancers. Yet, continued research efforts and clinical trials are still needed to confirm their potential as a standard treatment option, further understand their mechanisms of action, optimize dosing regimens, and explore potential combination therapies for improved patient outcomes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-024-03579-z.

Supplementary Material 1

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Author contributions

ZC, HY and TH conceived the study. HY, ZY and JS registered the protocol in PROSPERO. ZC and HY conducted the search strategy. ZC and JS completed screening on title and abstract and full text screening. ZC and HY completed risk of bias assessment. HY and ZY completed data extraction. ZC and TH completed data-analysis. ZC, HY and JS drafted the manuscript. ZC and TH reviewed the draft version of the manuscript. All authors reviewed, revised and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Agree to publish this article.

Competing interests

The authors declare no competing interests.

Author details

[1]Hangzhou Lin'an Traditional Chinese Medicine Hospital, Hangzhou, Zhejiang 311300, China
[2]General Internal Medicine Department, Tongde Hospital of Zhejiang Province, Hangzhou, Zhejiang 310012, China
[3]Hangzhou TCM Hospital of Zhejiang Chinese Medical University, Hangzhou Hospital of Traditional Chinese Medicine, Hangzhou, Zhejiang 310007, China
[4]Department of Oncology, Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou, Zhejiang 310007, China

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