REVIEW ARTICLE

Updates on DNA methylation modifiers in acute myeloid leukemia

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Abstract

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. Chemotherapy with cytotoxic agents is the standard of care, but is associated with a high rate of adverse events. Elderly patients are frequently intolerant to such treatment, presenting a very poor prognosis. The hypomethylating agents (HMA) azacitidine or decitabine represent one of the main therapeutic alternatives for these patients. Isocitrate dehydrogenase inhibitors (IDH) constitute another therapeutic class with DNA methylation effects in AML. In this article, we review the use of first- and second-generation HMA and IDH inhibitors in AML. The data collected demonstrated that HMA are generally considered effective and safe for AML patients who are not eligible for standard chemotherapy. The combination of azacitidine or decitabine with venetoclax was recently approved by the US Food and Drug Administration (FDA) for older AML patients and those unfit for intense chemotherapy. IDH inhibitors also showed encouraging results for relapsed/ refractory AML patients harboring an IDH mutation and received FDA approval. Therefore, recent studies have led to the emergence of new therapeutic options using HMA and IDH inhibitors for specific groups of AML patients, representing an important step in the treatment of this aggressive malignancy. New options should emerge from the ongoing studies in the coming years.

Keywords Acute myeloid leukemia · Hypomethylating agents · Clinical trials · DNMT inhibitors · IDH inhibitors

Introduction

Acute myeloid leukemia (AML) is caused by molecular alterations in hematopoietic stem and progenitor cells that favor greater cellular proliferation and reduced differentiation [1]. The median age at diagnosis is 68–72 years, and the highest mortality rates occur in older adults [2]. In the US, more than 10,000 deaths were estimated to have occurred due to AML in 2015 [3].

The genetic profile of leukemia cells influences the classification, prognosis, and treatment choice [4]. Patients with chromosomal translocations involving transcription factors that compose the core binding factor (CBF), i.e.: t(8;21)(q22;q22) *RUNX1/RUNX1T1* and inv (16)(p13q22) *CBFB/MYH11*, are usually associated with a favorable prognosis, as patients with a mutated nucleophosmin (*NPM1*). These patients usually experience favorable outcomes without the need of allogeneic hematopoietic stem-cell transplantation (HSCT). On the other hand, patients with complex cytogenetics, monosomal karyotype; t(9;22)(q34.1;q11.2) *BCR-ABL1*, inv.(3)(q21q26) *RPN1/MECOM*; t(6;9)(p23;q34.1) *DEK-NUP214*; t(v;11q23.3); − 5 or del (5q); − 7; − 17/abn(17p); mutated *RUNX1*; *ASXL1* or *TP53*, and *FLT3-ITD* with a high allele burden and wild-type *NPM1* have dismal outcomes, with median overall survival (OS) of 6–12 months, even with HSCT. Finally, patients without any of the aforementioned cytogenetics findings have an intermediate outcome, usually benefiting from HSCT [5].

Epigenetic changes also contribute to AML pathogenesis [6]. In fact, some of the AML recurring mutations occur in genes involved in the regulation of DNA methylation (*DNMT3A*, *DNMT3B*, *TET*, *IDH1*, *IDH2*) or histone acetylation (*EZH2*, *MLL*, *ASXL1*) [7]. These findings, together with the fact that epigenetic modifications are reversible, supported the rationale for the development of key clinical researches of novel epigenetic therapies in AML [6].

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AML treatment initially consists of attempting to obtain complete remission (CR) with induction chemotherapy, which usually involves daunorubicin at the dose of 60 or 90 mg/m^2 or idarubicin at the dose of 10–12 mg/m^2 for the first 3 days and infusion of 100–200 mg/m^2 of cytarabine daily from days 1 to 7, a regimen known as "7 + 3" [8, 9]. However, induction failures can occur in up to 40% of patients, depending on the patient's age [10], with a CR rate of 65–73% in young newly diagnosed AML patients and a CR rate of only 38–62% in patients over 60 years [11]. In order to eliminate possible remaining leukemia cells and prevent relapse, a consolidation (or post-remission) therapy is recommended with the following options: (a) a new course of chemotherapy or (b) HSCT. These strategies may be used separately or in combination, depending on the condition of the patient and the availability of a compatible donor [11]. For patients with a favorable prognosis, consolidation chemotherapy may be the preferred choice [8]. For the intermediate or adverse prognostic groups, HSCT remains the most effective long-term strategy [8]. Whether HSCT should be preceded by a consolidation course is still open for debate, particularly with the incorporation of measurable residual disease in clinical practice, with evidence suggesting either no benefit in patients who achieve CR after induction [12, 13] or an improvement in OS with a consolidation course prior to HSCT [14].

Patients unfit to receive standard chemotherapy may be treated with low dosages of cytarabine (LDAC) or hypomethylating agents (HMA) [15, 16]. LDAC have been the standard of care for patients ineligible to intensive therapy for more than 30 years. Although with CR rates around 20% and median overall survival (OS) around 90 days, complete responders seem to derive a benefit, with overall survival exceeding 18 months [16], which has led to the use of LDAC in several clinical trials assessing the efficacy of new drugs [17–19].

HMA are used as a standard treatment for patients with high-risk myelodysplastic syndromes (MDS) [20], and some of them have already been approved by the international regulatory agencies or are in an advanced phase of clinical trials to treat AML.

Despite the available treatments, a 5-year survival is only achieved by 40–45% of young patients and by less than 10% of elderly patients [21]. The development of new therapies is therefore of utmost importance for the reduction of refractory/resistant AML cases and to increase the quality of life and survival of patients [22, 23].

The aim of this review was to summarize the scientific literature on the use of HMA for AML, either approved or in clinical trials. We have reviewed HMA mechanisms of action and main results from clinical trials with AML patients, firstly focusing on decitabine and azacitidine and then newer HMA.

DNA methylation

DNA methylation consists in the enzymatic addition of a methyl (-CH3) group at the C5 position in cytosine [24]. The addition is catalyzed by the action of three enzymes: DNA methyltransferase 1 (DNMT1) – for the maintenance of methylation; and DNMT3A and DNMT3B – for de novo methylation [25].

Demethylation can occur through oxidation reactions catalyzed by the enzyme ten-eleven translocation (TET), more specifically the subtypes TET1, TET2, and TET3 [26, 27].

Cancer cells exhibit an abnormal methylation pattern which involves global hypomethylation and hypermethylation of promoter regions [28, 29]. In addition, mutations in the *DNMT3A* gene are present in approximately 10–25% of AML patients [7]. The most frequent mutation occurs at arginine 882 (R882), which is associated with increased proliferation of hematopoietic stem cells and resistance to conventional anthracycline chemotherapy [30].

Hypomethylating agents

DNMT inhibitors

The first DNMT inhibitors were studied in animal models for hematological diseases in the 1960s [31–33], and since then, research on this pharmacological class has been intensified, leading to the discovery of their multiple antineoplastic effects. These inhibitors were initially used as cytotoxic agents at high doses [34, 35] and later as low-dose epigenetic modifying agents [36–38].

Decitabine

Decitabine is a Food and Drug Administration (FDA)-approved drug for the treatment of adult patients with newly diagnosed or secondary AML.

Decitabine is a pro-drug analogous to nucleoside cytosine that generates the active metabolite decitabine triphosphate [36]. The metabolite is incorporated into the DNA during the S phase of the cell cycle for the formation of a covalent adduct with the DNMT enzymes and consequent inhibition of their activity. In addition, decitabine interferes in the synthesis of new DNA, damaging the cell proliferation and causing apoptosis [39]. Reduction of angiogenesis and accumulation of reactive oxygen species have also been reported [39, 40].

Clinical trials

Kantarjian et al. conducted a Phase 3 clinical trial of decitabine in AML elderly patients. Between January 2006 and April 2009, four hundred and eighty-five patients aged

65 or older were randomized into the decitabine group ($n =$ 242) or the physician's treatment of choice (TC) group ($n =$ 243: 215 for cytarabine and 28 for supportive care) [41].

Two analyses were performed at different time points, both with the participants being evaluated by intention to treat (ITT). The first analysis occurred in October 2009 with a median OS in the decitabine group of 7.7 months (95% CI, 6.2 to 9.2 months) compared to median OS in the TC group of 5 months (95% CI, 4.3 to 6.3 months, $p = 0.108$) and Hazard Ratio (HR) for death of 0.85 (95% CI, 0.69 to 1.04). In a second analysis with mature survival and updated safety data (October 2010), a statistically and clinically significant reduction in risk of death of 18% was observed in the decitabine group (HR = 0.82, 95% CI, 0.68–0.99, p-nominal = 0.0373). In addition, complete remission (CR) rate plus the CR rate without complete platelet recovery (CRp) was 17.8% in the decitabine group in comparison to 7.8% in the TC group. The incidence and severity of adverse events were similar between both groups, most of them related to myelosuppression [41].

Welch et al. evaluated the relationship between clinical response and mutation status in 84 AML or MDS patients. An extension cohort was included with 32 adult individuals with AML (24 and 8 patients received decitabine 20 mg/m^2 respectively for 10 days and 5 days in 28-day cycles) [42].

The CR rate and overall response rate (ORR) were reached by 15 (13%) and 53 (46%) patients, respectively. Exome or targeted gene panel sequencing was performed in 99 of the 116 patients. All 21 patients with *TP53* mutation presented clearance of bone marrow blasts (complete remission, complete remission with incomplete count recovery, or morphological leukemia-free state) compared to 32 of 78 patients (41%) with wild-type *TP53* ($p < 0.001$). Patients with unfavorable cytogenetic risk also showed a higher response rate compared to patients with intermediate or favorable cytogenetic risk (67% vs. 34%, $p < 0.001$). However, responses were not durable, and relapse in patients with *TP53* mutation occurred with the outgrowth of a preexisting subclone. The most common adverse events were related to neutropenia and thrombocytopenia [42]. Overall, decitabine treatment seemed effective and well tolerated in patients who do not tolerate intensive chemotherapy or who harbored *TP53* mutation. Observational studies will be important to confirm these findings in a real-life setting.

Regarding maintenance therapy, Blum et al. [43] evaluated decitabine in young adults in complete remission who had previously been treated with induction or consolidation chemotherapy. One hundred and thirty-four patients received decitabine, and most of them presented favorable or intermediate cytogenetic risk. Despite severe and frequent adverse events, there was no death-related toxicity. In addition, even with 79% of the patients presenting grade 4 neutropenia, only 4% had grade ≥ 3 infections. The authors then concluded that, overall, patients tolerated the therapy well. Disease-free survival (DFS) in 1 year was 79% (95% CI, 71–85%) and in 3 years was 54% (45–62%); OS was 96% (90–98%) in 1 year and 68% (59–75%) in 3 years. When compared with a historical reference group, decitabine as maintenance therapy showed no apparent benefit. According to the authors, the chosen dosage may have diminished the efficacy of the drug [43]. It is worth pointing out that the treatment schedule according to the package label is 20 mg /m^2 in 5 days, repeated every 4 weeks, and the schedule used in the study was 4–5 days of 20 mg/m^2 decitabine every 6 weeks.

He et al. conducted a meta-analysis about the efficacy and safety of decitabine as monotherapy in previously untreated AML patients over 60 years old. Nine clinical studies, published between 2010 and 2016, with different therapeutic regimens were included (a total of 718 patients). Myelosuppression was the most common adverse event. Infection rate was 36%, and the rate of early death (ED) was 7% at 30 days and 17% at 60 days [44].

The combined estimate of the studies resulted in values of 27% of CR (95% CI, 19–36%), ORR of 37% (95% CI, 28%–47%), and OS of 8.09 months (95% CI, 5.77–10.41). The outcomes varied according to the dosage adopted, and the administration of decitabine for 10 days every 4 weeks presented the best responses. The CR rate in this group was 45% (95% CI, 37–54%), ORR of 53% (95% CI, 37–70%), and OS of 11.30 months (CI 95%, 8.26–14.34). Subgroup analysis by age, cytogenetic risk (intermediate versus adverse), type of AML (de novo versus secondary), and percentage of bone marrow blasts (< 30% versus > 30%) revealed no statistical differences, indicating a homogeneous action of decitabine. A limitation of the study was lack of comparative data with conventional therapy (low-dose chemotherapy) [44].

Azacitidine

Azacitidine is a cytidine nucleotide analog, a substrate of kinases for the generation of active metabolites: 5-azacitidine-5′-triphosphate (5-aza-CTP) and decitabine triphosphate (5-azaC – dCTP) [45]. Unlike decitabine, azacitidine also has effects on RNA. Its action is related to the inhibition of the methylation of the tRNA by the decrease in the levels of tRNA methyltransferase (DNMT2), impacting the protein synthesis and causing apoptosis [46, 47].

Clinical trials

We have selected two multicenter Phase 3 studies employing azacitidine subcutaneously in AML.

Fenaux et al. evaluated azacitidine effects in a trial including 358 patients with high-risk MDS (maximum 30% bone marrow blasts) or chronic myelomonocytic leukemia (CMMoL). However, according to the WHO classification for AML (starting from 20% of blasts in the bone marrow), approximately one-third of the selected patients had in fact

AML with low blast counts. One hundred and seventy-nine subjects were randomized to receive azacitidine, and the same number of patients received conventional treatment (supportive care, low-dose cytarabine, or intensive chemotherapy). The median age of the patients was 69 years, with a predominance of elderly individuals over 65 years and intermediate or adverse cytogenetic risk [48].

Considering the entire group (MDS, CMMoL, and AML patients), the median OS was 24.5 months for the azacitidine group and 15 months for the conventional treatment group, resulting in a difference of 9.4 months with a hazard ratio for OS of 0.58 (95% CI, 0.43–0.77, $p = 0.0001$). HMA benefits were observed in the three cytogenetic groups: favorable, intermediate, and poor risk. Time to disease progression, relapse after complete or partial remission, and death were statistically longer in the test group (median of 14.1 months, IQR 4.2–27.6) than in the control group (median 8.8 months, 3.8 – not reached; log-rank $p = 0.047$). Neutropenia, thrombocytopenia and anemia were the most common grade 3 or 4 adverse events. The authors concluded that the HMA therapy was effective in patients with MDS and AML with less than 30% of blasts. In the subgroup analysis of treatment (azacitidine vs. supportive care, azacitidine vs. low-dose cytarabine, and azacitidine vs. intensive chemotherapy), azacitidine showed a statistically significant difference in OS when compared to the low-dose cytarabine and supportive care. Azacitidine showed no statistical difference in OS and CR compared to intensive chemotherapy; however, the number of patients in this group was reduced ($n = 25$), limiting the power of the comparison [48].

Dombret et al. conducted a study to evaluate the effects of azacitidine in 488 elderly AML patients with blast count above 30% and intermediate or adverse cytogenetic risk. Two hundred and forty-one patients were randomized to receive the test drug, and 247 to receive the conventional treatment (supportive care, standard induction, or low-dose cytarabine chemotherapy) [49].

The median OS for azacitidine group was 10.4 months (95% CI, 8.0–12.7 months) compared to 6.5 months in the control group (95% CI, 5.0–8.6 months) (HR = 0.85, 95% CI, 0.69–1.03, $p = 0.1009$). In a second analysis, in which patients who received subsequent therapies were censored, the median OS in the first group was 12.1 months (95% CI, 9.2–14.2 months) vs. 6.9 months (95% CI, 5.1–9.6 months) in the second group (stratified HR, 0.76; 95% CI, 0.60–0.96; $P = 0.0190$). The 1-year survival rate was 50.7% with azacitidine vs. 37.7% for conventional treatment, with a difference of 13% (95% CI, 3.3%–22.7%). The CR + CR rate with incomplete recovery of blood cells was 27.8% vs. 25.1% with no statistical difference. The drug was considered well tolerated. Importantly, in the univariate and multivariate regression analysis, the median OS of patients with adverse risk was twice the observed in the conventional treatment group (6.4 vs. 3.2 months, $p = 0.0185$). Overall, the authors concluded that azacitidine induced a clinically significant

improvement and may be an additional treatment option for elderly patients [49].

The data presented above emphasizes how azacitidine and decitabine use in clinical practice represented a progress in the treatment of AML, particularly in the elderly population. They were the first drugs in AML to target epigenetic mechanisms, with excellent responses in subsets of high-risk patients, such as those with *TP53* mutations. However, these responses have not been sustained, and most patients have not achieved a complete hematological response. Furthermore, azacitidine and decitabine have not been directly compared against each other in a randomized controlled trial in the setting of AML. Combination therapy of HMAs with recently approved agents, including epigenetically targeted therapies, is a promising approach which has yet to be tested in clinical trials.

Venetoclax (ABT-199) plus decitabine or azacitidine

Venetoclax is an oral inhibitor of the proapoptotic protein B cell lymphoma 2 (BCL-2) that has showed a synergistic effect when combined to azacitidine in myeloid cells in vitro [50].

Clinical trials

A multicenter, phase 1b dose-escalation and expansion study included 145 elderly treatment-naive AML patients and ineligible for intensive chemotherapy to evaluate the combination of venetoclax with decitabine or azacitidine. Decitabine (20 mg/m^2 for 5 days) or azacitidine (75 mg/m^2 for 7 days) was administered with venetoclax (at doses of 400, 800, or 1200 mg per day). The rate of CR + CR with incomplete count recovery was 67% in all venetoclax doses and 73% in the venetoclax 400 mg plus HMA cohort. The median OS was 17.5 months (12.3 – not reached) for all patients, and it was not reached (NR) (11.0 – NR) for the venetoclax 400 mg + HMA cohort. The most common adverse events were gastrointestinal and hematological. The association was considered well tolerated and effective [51].

Due to the promising results and important unmet medical need, FDA granted accelerated approval for venetoclax + azacitidine or decitabine or low-dose cytarabine for elderly patients with AML (≥ 75 years) or who have comorbidities that preclude the use of intensive induction chemotherapy. It is of utmost importance to validate these findings in a randomized, controlled clinical trial, and two Phase 3 trials are ongoing (NCT02993523 and NCT03069352).

Guadecitabine (SG1-110)

Guadecitabine is a second generation HMA structurally developed to be more resistant to cytidine deaminase (responsible for HMA degradation) and consequently increase the rate of responders and treatment efficacy [52].

Clinical trials

An open-label, randomized, Phase 1 trial evaluated the safety and the most appropriate posology for the treatment of patients with MDS ($n = 19$) or refractory or relapsed AML ($n = 74$) after standard treatment by dose escalation. The study showed that guadecitabine was generally well tolerated, and the most appropriate regimens chosen for the Phase 2 study were 60 or 90 mg/m^2/day for 5 consecutive days in 28-day cycles [53].

A multicenter, open-label, randomized, Phase 2 trial evaluated different dosages of guadecitabine in treatment-naïve elderly patients (≥ 65 years) with relapsed or refractory MDS or AML who did not tolerate standard chemotherapy. The subjects were randomized to receive guadecitabine 60 mg/m^2 during 5 days ($n = 26$); guadecitabine 90 mg/m^2 ($n = 28$) during 5 days; or guadecitabine 60 mg/m^2 during 10 days ($n = 53$) [54].

Both groups of 5 and 10 days presented similar OS (10.5 vs. 9.5 months, respectively); however, the 5-day regimen group appeared to have benefited more due to the lower incidence of serious adverse events [54].

A Phase 3 randomized study (NCT02348489) comparing guadecitabine to treatment choice (azacitidine, decitabine, or low-dose ARA-C) has recently been completed. The trial included 815 treatment-naïve AML patients not eligible for intense chemotherapy. It failed to meet the primary endpoints of statistically significant advantage of guadecitabine over treatment choice for CR rate and OS, suggesting that guadecibine has an overall similar efficacy and safety compared to standard therapy [55].

In the two arms, the patients received a median of five treatment cycles. However, many patients (approximately 40% in both arms) received ≤ 3 treatment cycles mainly due to early death or progression. Survival analysis of the patients who received more than 3 treatment cycles showed a potential benefit of guadecitabine vs. treatment choice. Median, 1-year OS, and 2-year OS were 15.6 months, 60 and 29% on the guadecitabine group versus 13 months, 52 and 20% on the treatment choice group; log-rank p value = 0.02, HR 0.78, 95%CI, 0.64–0.96. A potential benefit was also observed in patients who achieved any CR (CR, CRp, or CRi) [55].

Other Phase 3 trials with guadecitabine (SGI-110) in patients with relapsed and refractory acute myeloid leukemia are in progress.

Although the aforementioned Phase 3 trial failed, it may be possible that some specific group could benefit from the drug. Therefore, further studies will be important to elucidate this issue.

IDH inhibitors

IDH1 and IDH2 are considered important therapeutic targets since mutations in these genes are found in approximately 20% of AML patients [56]. IDH inhibitors aim to reduce the amount of mutant IDH proteins and, consequently, reducing the levels of the oncometabolite 2-hydroxyglutarate (2-HG). The conversion of a-ketoglutarate (α-KG) to 2-HG oncometabolite by mutant IDH proteins inhibits α-ketoglutarate-dependent enzymes such as TET proteins that mediate DNA demethylation, indirectly leading to a dysregulation of methylation [57].

Enasidenib (IDH2 inhibitor) and ivosidenib (IDH1 inhibitor) have already been approved by FDA. Other IDH inhibitors are in initial clinical development.

Enasidenib

Enasidenib (AG-221) is an oral, first-in-class IDH2 inhibitor which is currently undergoing Phase 3 clinical trials (clinicaltrials.gov). Due to promising results, the FDA has granted the approval of Idhifa® (enasidenib) registry in August 2017 for patients with relapsed or refractory AML harboring the mutant gene [58].

The first clinical study was an open-label phase 1/2 trial to assess safety and dosage. The dose-escalation phase included 113 adult patients with AML or MDS with refractory anemia and excess blasts harboring an IDH2 mutation. The maximum tolerated dose (MTD) was not reached. However, 5 out of 7 patients in the 650 mg dose group presented significant adverse events, which led to dose reduction. Based on the pharmacokinetics, clinical activity, and inhibition of 2-HG levels, the dose of 100 mg once a day was chosen to be administered during the second part of the study (expansion phase) [59]

The expansion phase included 126 patients divided into four cohorts: (1) elderly (> 60 years) with recurrent or refractory AML or at any age when relapsing after HSCT; (2) patients < 60 years with refractory disease or relapse without history of HSCT; (3) elderly (> 60 years) with untreated AML and ineligible for induction chemotherapy; and (4) patients ineligible for the previous groups. Considering all the participants in the study ($n = 239$), the majority presented intermediate cytogenetic risk with ECOG performance between 0 and 2 and median age of 70 years [59].

All 239 patients were evaluated for safety outcomes. Treatment-related grades 3 to 4 adverse events were hyperbilirubinemia, hematological events, differentiation syndrome associated with the IDH inhibitor (IDH-SD), and infections. Clinical outcomes were described for the relapsed or refractory AML subgroup. In this subgroup, ORR was achieved by 40.3% (95% CI, 33.0–48.0%) of the patients (considering Phases 1 and 2) and 38.5% (95% CI, 29.4–48.3%) of the patients who received a dose of 100 mg per day. Median OS was 9.3 months (95% CI, 8.2–10.9 months). Importantly, the results suggested that enasidenib exerts activity on both IDH2 mutations (IDH2-R140 and IDH2-R172) [59].

Ten percent of the patients proceeded to bone marrow transplantation. In a subsequent analysis, clinical The authors believe that the drug could be a bridge for a potential cure. It is noteworthy that the majority of patients who exhibited reduced levels of 2-HG did not reach clinical response, suggesting that 2-HG decrease is not a predictive of response. Hematologic toxicity was low and may be an advantage over intensive chemotherapy and other treatments [59].

In a subsequent analysis, clinical response to enasidenib reflected the number of mature neutrophils and a low index of infection. In addition, patients who achieved CR or PR harbored fewer mutations than the nonresponders ($p < 0.001$) and individuals with mutations in NRAS achieved less CR ($p = 0.0114$), whereas patients with mutations in the MAPK signaling pathway (mPTPN11) did not respond to treatment [60]. Other clinical trials, including Phase 3 are ongoing (clinicaltrials.gov).

Enasidenib has some advantages compared to the standard chemotherapy, presenting clinical response with differentiation of malignant cells and oral form. It is the first targeted therapy for AML with IDH2 mutation, representing an important step in the precision medicine and a possible adjuvant to chemotherapy in some patients. Importantly, part of the patients proceeded to bone marrow transplantation. Despite the promising results obtained in this Phase 2 trial, a randomized and controlled Phase 3 trial remains to be completed. There are some ongoing clinical trials evaluating the association of enasidenib with other drugs, which will be useful to determine potential synergistic effects.
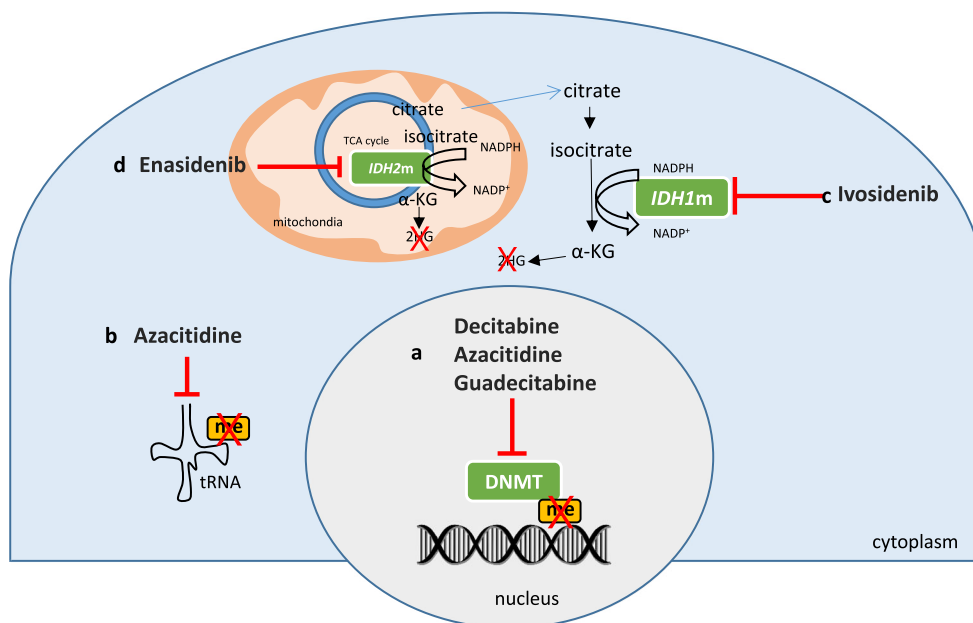
Ivosidenib

The first-in class small molecule IDH1 inhibitor ivosidenib (AG-120) received FDA approval for the treatment of relapsed or refractory AML with susceptible IDH1 mutation after the results achieved in a Phase 1 trial [61, 62]. The study was multicenter, non-randomized, open label, single arm, dose escalation, and dose expansion. Two hundred and sixty-eight patients were enrolled, of which 179 had relapsed or refractory AML and received the starting dose of 500 mg of ivosidenib daily [61].

Ivosidenib was quickly absorbed and the mean plasma 2-HG levels reached similar levels of healthy individuals after multiple doses of 500 mg daily. MTD was not defined. The majority (98.9%) of the patients with relapse or refractory AML presented an adverse event, including IDH differentiation syndrome, grade 3 or higher leukocytosis and a serious adverse event of prolongation of the QT interval. No treatment-related adverse event leading to death was observed in these patients [61].

CR or CR with partial hematologic recovery (CRh) was reached by 30.2% (95% CI, 23.5–37.5) of the 179 patients with relapse or refractory AML. Median length of response was 6.5 months (95% CI, 5.5–11.1) and median time to reach CR or CRh was 2 months (range: 0.9–5.6 months). CR or CRh responders showed decreased levels of IDH1 mutations in bone marrow mononuclear cells and neutrophils during the course. All the 7 patients with clearance of IDH1 mutations achieved complete remission [61]. Transfusion independence was achieved by approximately 37% of the patients who previously presented red blood cell and/or platelet transfusion-dependence [61].

Fig. 1 Mechanism of action of the reviewed HMA and IDH inhibitors. **a** Decitabine, azacitidine and guadecitabine metabolites are incorporated into the DNA to form an adduct with DNMT, inhibiting the DNA methylation. **b** Azacitidine metabolite incorporates into tRNA and also inhibits tRNA methylation. **c** Ivosidenib and **d** enasidenib respectively inhibit the mutated forms of IDH1 and IDH2 (IDH1m and IDH2m), which induce the abnormal production of the oncometabolite 2-hydroxyglutarate (2HG)

In conclusion, ivosidenib monotherapy was considered well tolerated and effective for relapsed or refractory AML patients harboring IDH1 mutation. Like enasidenib, this is an oral first-in class drug that represents a major advance in the targeted AML treatment. QT prolongation and IDH differentiation syndrome must be monitored during treatment. Randomized, comparative Phase 3 trials are necessary to confirm the efficacy and safety. Double-blind, randomized and placebo-controlled Phase 3 trials are ongoing to evaluate the combination of ivosidenib with other drugs (clinicaltrials.gov).

Conclusion

Dysregulation of DNA methylation is a hallmark of AML and numerous preclinical and clinical studies testing DNA methylation modifiers in this malignancy have been conducted, including hypomethylating agents and IDH inhibitors. Here we have briefly reviewed the mechanism of action (Fig. 1) and the results from clinical trials of different HMA and IDH inibitors in AML patients.

HMA have demonstrated efficacy in clinical studies, prolonging survival when compared to low-dose chemotherapy or best supportive care. The combination of HMA plus venetoclax yielded a high response rate in a Phase 1b trial with older AML patients ineligible for intense chemotherapy. IDH inhibitors were also effective for relapse or refractory AML patients in a Phase 1/2 trial. The drugs herein being evaluated presented several adverse events; nevertheless, they were generally considered tolerable.

Further clinical trials are needed for a clear evaluation of HMA and IDH inhibitors in AML. Considering the unique mutation profile of each patient, the future approach to AML and other cancers is more likely to be through the combination of different therapeutic classes, in order to target diverse molecular pathways and prevent the emergence of pharmacological resistance.

Compliance with ethical standards

Conflict of interest Bruna Contieri declares she has no conflicts of interest. Bruno Kosa Lino Duarte declares he has no conflicts of interest. Mariana Lazarini declares she has no conflicts of interest.

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