FLT3 and IDH1/2 Inhibitors for Acute Myeloid Leukemia: Focused Clinical Narrative Review of Forthcoming Drugs from an Indian Context

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Abstract

Therapeutic approaches for acute myeloid leukemia (AML) have witnessed minimal evolution in recent decades, primarily relying on advancements in supportive care and transplantation to drive improvements in overall survival rates. However, treatment with intensive chemotherapy may not be feasible for patients with advanced age or reduced fitness, and outcomes for patients with relapsed/refractory disease continue to be suboptimal. Several agents with a novel mechanism of action have been developed in the past decade and have shown efficacy in patients with both newly diagnosed and relapsed AML. Out of these, several FLT3 (FMS like tyrosine kinase 3) and IDH1/2 (isocitrate dehydrogenase 1/2) inhibitors have received regulatory approval in specific clinical settings and are available for clinical use. This is an actively expanding field with several ongoing clinical trials in advanced phases. We provide a focused narrative review of drugs from these two categories with available clinical data.

Keywords
- myeloid
- leukemia
- FLT3
- midostaurin
- gilteritinib
- sorafenib

Introduction

Drug therapy for acute myeloid leukemia (AML) has remained largely unchanged since the introduction of the "7 + 3" regimen in 1973, with most of the subsequent improvement in survival attributable to advances in supportive care, infection control, and allogeneic stem cell transplantation.[1,2] Risk-adapted use of intensive chemotherapy and stem cell transplantation following induction now allows 30 to 50% of younger, medically fit patients to achieve long-term cure.[3,4] Despite these advances, reliance on intensive chemotherapy presents several challenges that prevent optimal outcomes in specific clinical settings. First, intensive chemotherapy is often precluded by advanced age, reduced patient fitness, and/or financial limitations. A significant proportion of patients older than 60 years of age may not be candidates for intensive therapy and receive hypomethylating agents alone.[5] Improvements in survival over the past few decades have eluded older patients with AML, even in developed nations and necessitate newer nonchemotherapy approaches.[6] Second, relapsed or refractory disease is still associated with a poor long-term survival worldwide and is expected to benefit from newer therapies, similar to other hematologic malignancies.[7]

Several of these challenges are addressed by targeted oral agents, which represent the first drug approvals for AML in the past few decades. These small molecule inhibitors have demonstrated efficacy in both newly diagnosed and relapsed settings and are gradually transitioning to first-line therapy in combination or even as monotherapy, offering a new treatment approach for unfit patients who would not receive any treatment in the past.[4,8] These advances are relevant for India, where despite a lower age of presentation, physiological frailty is evident and very few patients over the age of 60 years

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receive intensive chemotherapy with curative intent.[5] Further, survival after relapsed disease in India is suboptimal, with low rates of allogeneic stem cell transplantation, warranting the introduction of newer, less toxic treatment options.[9]

Oral agents for AML are categorized based on their distinct cellular targets, each exhibiting unique mechanisms for efficacy and toxicity. We present a succinct and targeted review that incorporates the available supporting evidence and clinical application of presently accessible targeted oral agents (FMS like tyrosine kinase 3 [FLT3] inhibitors and isocitrate dehydrogenase 1/2 [IDH1/2] inhibitors) for AML.

Isocitrate Dehydrogenase Inhibitors

Cellular Mechanism

IDH enzymes catalyze the conversion of isocitrate to α-ketoglutarate (α-KG) by oxidative decarboxylation along with simultaneous reduction of NADP to NADPH. IDH1 and IDH2 are isozymes with significant sequence similarity and are mutated in several malignancies.[10] IDH3 is structurally distinct and does not have a defined pathogenic role at present. Relevant mutations in *IDH1* and *IDH2* were first identified in 2011, and since then have been consistently demonstrated at a frequency of 10 to 20% in patients with AML.[11,12] Mutations in *IDH1/2* modify the metabolic pathway to produce R-2- hydroxyglutarate instead of α-KG, leading to inhibition of several α-KG-dependent enzymes. This leads to a cellular differentiation block by inhibiting several enzymes involved in histone and DNA methylation.[13] Downstream effects from altered cell differentiation and cell cycle control promote leukemogenesis in vitro and are viable targets for inhibition in patients with AML.[14] Both IDH1 and IDH2 mutations have a similar mechanism of contributing to pathogenesis of AML. T Common point mutations noted in IDH1 and IDH2 are R132H and R172K, respectively, and are mutually exclusive.

Enasidenib

IDH2 mutations are noted in approximately 10 to 12% of patients with AML and frequently occur along with mutations in genes affecting epigenetic pathways (*ASXL1*, *SRSF2*, *RUNX1*, and *STAG2*).[15] Enasidenib is a selective *IDH2* inhibitor that was first shown to be effective in mouse xenograft models, significantly reducing cellular 2-KG levels, promoting cellular differentiation and improving survival.[16] Its safety and clinical activity as monotherapy was documented in a phase 1b dose escalation study, which included 239 patients with relapsed AML. An overall response rate (ORR) of 40.4% and a complete remission (CR) rate of approximately 19.3% was observed, with a median time to CR of 3.8 months (range, 0.5–11.2). Median overall survival (OS) was 9.3 months, with survival at 1 year of approximately 39%.[17] The most significant nonhematologic toxicity was differentiation syndrome (DS), observed in approximately 8% of patients. Further analysis of these data indicated that DS was more likely in patients with higher bone marrow blast counts and typically observed after a median of 30 days (range, 7–129) from starting treatment. Importantly, DS was reversed with temporary cessation of enasidenib and early initiation of steroids in all patients.[18]

Enasidenib exhibited effectiveness as a standalone treatment as well in 37 patients in the above cohort with previously untreated IDH2-mutated AML who were not eligible for standard therapy. In this cohort with a median age of 77 years, an ORR of 37.8% and CR of 19% was observed. Median OS was 10.4 months, indicating potential efficacy as first-line monotherapy.[19]

A recent phase 3 trial (IDHentify) evaluated patients older than 60 years of age with relapsed or refractory disease after failure of at least two lines of therapy. A total of 267 patients underwent randomization, with equal distribution between the enasidenib group and the conventional low-dose therapy group. Although no statistically significant disparities in OS were identified (6.8 vs. 6.2 months), the enasidenib cohort exhibited higher rates of complete response (26 vs. 3%) and ORR (41 vs. 11%).[20] A recent update of these data presented in the 2022 American Society of Clinical Oncology (ASCO) meeting showed a specific OS advantage for patients with the R172 mutation (14.6 vs. 7.8 months), which was not seen with patients with R140 mutations.[21]

Based on efficacy in patients with newly diagnosed AML, enasidenib was evaluated in a pragmatic combination with azacytidine in a phase II trial including patients with IDH2-mutated AML. A total of 26 patients were included (19 relapsed and 7 newly diagnosed) to receive enasidenib and azacytidine, with concomitant FT3 inhibitors and venetoclax allowed. Cumulative CR was noted in 100% of newly diagnosed patients and 58% with relapsed/refractory disease. This combination was well tolerated with a 6-month OS of 70% in newly diagnosed patients with median OS not reached after 11 months of follow-up period.[22] Comparable outcomes were achieved in a multicenter phase 2 trial that randomized participants to receive either azacytidine alone or in combination with enasidenib. The combined therapy demonstrated a notably superior ORR of 74% compared with 36% in the azacytidine monotherapy group.[23]

Of significant clinical interest, enasidenib was found to be safe in combination with venetoclax for pretreated patients with IDH2-mutated AML, showing an ORR of 55%.[24] Further dose finding studies of this combination are ongoing.

Ivosidenib

Ivosidenib (AG-120) was the first in-class IDH1 inhibitor developed with activity against several solid tumors.[25] It's clinical activity in AML as monotherapy was documented in a phase 1 study including 258 patients with relapsed/refractory disease following a median of two prior lines of therapy.[26] The rate of CR + CR with incomplete count recovery (CRi) was 30%, with median time to CR of 2.7 months and median OS of 14.5 months. It was well tolerated with the most common nonhematologic toxicities being QTc prolongation (7.8%) and DS (3.9%). Based on these data, it received U.S. Food and Drug Administration (FDA) approval in 2018 for patients with relapsed/refractory *IDH1*-mutated AML.

Ivosidenib also demonstrated single-agent activity in newly diagnosed patients ineligible for standard

chemotherapy (median age, 76 years), with CR + CRi rates of 42.4% and a median OS of 12.6 months.[27] It's safety and activity in combination with azacytidine in a phase 1b trial in patients with IDH1-mutated AML formed the basis for the randomized phase 3 AGILE trial, which led to regulatory approval for newly diagnosed patients in this setting.[28,29] This trial included 146 newly diagnosed patients who were randomized to azacytidine alone or in combination with ivosidenib. Combination therapy was associated with a higher median OS (24 vs. 7.9 months) and lower risk of treatment failure, relapse, or death (hazard ratio [HR] = 0.33, 95% confidence interval [CI] = 0.16–0.69) compared with azacytidine alone. Unique nonhematologic adverse effects in the ivosidenib arm included QT prolongation in 20% and DS in 14% patients. Following the evidence from these findings, the FDA granted approval to ivosidenib in May 2022 for its utilization in combination with azacytidine as a treatment option for newly diagnosed patients with IDH1-mutated AML.

Ivosidenib and enasidenib are also being evaluated in combination with intensive cytotoxic chemotherapy in newly diagnosed patients with *IDH1/2*-mutated AML. In 2021, the publication of phase 1 data presented findings from a study involving a cohort of 60 patients who received ivosidenib and 91 patients who received enasidenib in combination with intensive chemotherapy.[30] This study observed CR in 55 and 47% and CRi in 72 and 63% patients with ivosidenib and enasidenib, respectively. The median OS in the ivosidenib cohort was not reached and with enasidenib was 25 months. Among patients achieving CRi, minimal residual disease (MRD) negativity was noted in 80 and 63%, respectively. This study indicated the feasibility of adding IDH1/2 inhibitors along with intensive chemotherapy for newly diagnosed patients.

Ivosidenib is metabolized by the CYP3A4 enzymes, and drug toxicity can potentially increase in the presence of strong CYP3A4 inhibitors such as posaconazole and voriconazole. The manufacturer recommends reducing the dose to 250 mg once a day when used with concomitant azoles due to a higher risk of QTc prolongation.[31] However, a population pharmacokinetic analysis observed that increasing area under the curve (AUC) in the presence of azoles was not associated with an increase in clinical toxicity, likely indicating a wide therapeutic window.[32] As a result, the current expert opinion is to exercise "caution" in the presence of azoles and monitor the QTc interval closely while continuing the drug at the full dose of 500 mg per day.[33]

No significant safety concerns were highlighted on using a combination of ivosidenib with azacytidine and venetoclax in a phase Ib/III study, indicating a potentially new combination for IDH1-mutated AML.[34]

Olutasidenib

Olutasidenib (FT-2102) is a potent, selective IDH1 inhibitor, designed to induce differentiation of cells with mutated IDH1.[35] It was first evaluated in a phase 1 trial including 31 patients with IDH1-mutated AML or MDS, where an ORR of approximately 33% was documented.[36] Dose escalation and safety of combination with azacytidine was subsequently evaluated in a similar patient population, where an ORR of 39% for single agent and 54% for combination therapy was noted. Importantly, 40% patients had mutation clearance, with mIDH1 Variant Allele Frequency (VAF) of <1% after treatment. DS was observed in 13% patients, which was reversible with drug discontinuation.[37]

The phase 1 component of a multicenter trial (NCT NCT02719574) evaluating olutasidenib was published in 2022, including patients with IDH1-mutated AML or MDS both as single agent ($n = 32$) and in combination with azacytidine ($n = 46$) For patients with relapsed AML, ORR of 41% as monotherapy and 46% as combination were observed.[38] For treatment-naïve patients, response rates of 25% for monotherapy and 77% for combination were observed.

The phase II component of the multicenter trial planned to evaluate the efficacy of olutasidenib both as single agent and in combination with azacytidine for patients with AML/MDS. The final analysis included 153 patients with IDH1-mutated AML after a median of two lines of therapy, of which 147 were evaluable. In this subset, monotherapy with 150 mg twice a day was initiated, with ORR of 48% and CR + CRi rates of 35%. The median duration of overall response was 11.7 months and median OS was 11.6 months.[39] Based on this study (2102-HEM-101), olutasidenib received FDA approval in December 2022 as monotherapy for patients with relapsed/refractory AML at a dose of 150 mg twice a day.

Phase 2 data on treatment-naïve patients was presented in 2021, in which patients were divided into four cohorts based on prior therapy and exposure to IDH1 inhibitors or Hypomethylating agents (HMAs).[40] In treatment-naïve patients, ORR of 64% and CR of 45% was documented. In R/R disease without previous HMA or IDH1 inhibitor exposure, similar response rates and median CR duration of 16 months was documented.

FMS-Like Tyrosine Kinase 3 Inhibitors

Cellular Mechanism

FLT3 is a receptor kinase required for hematopoietic cell proliferation and differentiation.[41] The presence of FLT3 mutations was initially discovered in patients with AML in 1996, and since then, it has been recognized as one of the most frequent mutations observed in AML. Approximately 25% of all patients with AML have the FLT3 internal tandem duplication (FLT3-ITD) and 5% have a tyrosine kinase domain (FLT3-TKD) mutation.[42] The pathogenic mechanism of the FLT3-ITD mutation is complex and is described in a succinct review by Friedman et al.[43] FLT3-ITD mutations give rise to the dissociation of the intracellular juxtamembrane domain from the FLT3 receptor, resulting in persistent downstream activation of phosphorylation and subsequent cellular proliferation.

Mutations in FLT3 do not lead to an AML phenotype in isolation, indicating that these mutations are late events with a greater role in altering disease phenotype than disease initiation, in contrast to BCR/ABL1 mutations in chronic myeloid

leukemia.[44] Most initial studies therefore focused on combining FLT3 inhibitors with standard treatment rather than as monotherapy. FLT3 mutations also have a role in posttransplant relapse, providing an impetus for several studies using FLT3 inhibitors in posttransplant maintenance.[45]

First-Generation Inhibitors

Sorafenib, midostaurin, lestaurtinib, and sunitinib are among the first-generation FLT3 inhibitors, characterized by their ability to inhibit multiple kinases. As a result, several off target adverse events are noted with this group of drugs.[46]

Sorafenib

Sorafenib, an orally administered multikinase inhibitor, was developed in 2001 and subsequently gained approval for the treatment of various solid tumors. It was first demonstrated to have activity against AML cell lines in vitro in 2008, indicating potential clinical benefit. Importantly, sorafenib-induced apoptosis in AML was synergistic with cytarabine and BCL2 inhibitors.[47] Clinical activity and safety of sorafenib was demonstrated in a phase I study including 50 unselected patients with advanced MDS or relapsed acute leukemias. A significant reduction in blast count, especially in FLT3-mutated AML was observed with sorafenib monotherapy.[48] As a synergistic action with chemotherapy was known, further clinical studies were largely performed as part of combination therapy.[49]

Sorafenib was shown to be safe and effective in combination with intensive chemotherapy with idarubicin and cytarabine in a phase I/II study including 51 patients. The initial rates of CR were promising, being 75% for the overall cohort and 93% in those with FLT3 mutations.[50] Further follow-up of this study included 62 patients and confirmed a higher rate of initial CR and CR with Partial count recovery (CRp) in patients with FLT3 mutations (95 vs. 83%) but failed to show a durable clinical benefit. Survival was inferior among patients with FLT3 mutations compared with wild type FLT3, with OS of 15.5 vs. 42 months and DFS of 9.9 vs. 17.3 months, primarily owing to high rates of relapse in this subgroup.[51] A similar combination also failed to show any advantage of adding sorafenib to intensive chemotherapy in a randomized trial including 200 newly diagnosed patients unselected for FLT3 mutations.[52]

The SORAML trial, a recent randomized study, featured sorafenib in combination with intensive chemotherapy and enrolled newly diagnosed patients below the age of 60. This phase 2 trial examined the effects of sorafenib in the specified patient population, including 276 patients (chemotherapy + sorafenib 134, chemotherapy + placebo 133). Patients were not selected for FLT3 mutations, which were present in 17% of patients in both arms. There was no significant difference in rates of CR among both arms (60 vs. 59%). After a median follow-up of 36 months, median event-free survival (EFS) was higher with sorafenib (21 vs. 9 months), but there was no difference in OS. A nonsignificant difference in EFS was noted in patients with FLT3 mutations (18 vs. 6 months). However, there was a significantly higher risk of hand–foot syndrome, diarrhea, and cardiac events in the sorafenib group.[53] Updated analysis published in 2021 after a median follow-up of 78 months demonstrated the sorafenib arm to have a higher EFS (41 vs. 27%) and relapse-free survival (53 vs. 36%) without any OS advantage (5-year OS 63 vs. 51%).[54]

The evaluation of sorafenib's effectiveness in a patient population with a high prevalence of FLT3 mutations has solely relied on a retrospective study encompassing 183 patients, with a median age of 52 years. Patients were compared based on whether the initial therapy was intensive chemotherapy alone or with sorafenib. After propensity matching, addition of sorafenib demonstrated a higher ORR (99 vs. 83%), similar rates of CR (79 vs. 74%), and a higher OS (42 vs. 13 months). As most of the above studies have not shown a uniform clinical benefit in a prospective setting, sorafenib is currently not approved for routine use in AML. Prospective studies including patients enriched for FLT3 mutations are expected to provide a clearer picture of its clinical efficacy.

Sorafenib is presently undergoing evaluation as an integral component of standard therapy for patients who have recently been diagnosed (NCT05404516) and as an adjunct to conditioning in the context of stem cell transplantation (NCT03247088).

Midostaurin

Midostaurin, classified as a first-generation multikinase inhibitor, exhibits inhibitory effects on FLT3, vascular endothelial growth factor receptor-2, c-kit, platelet-derived growth factor receptor-α (PDGFRα), and PDGFRβ. The clinical efficacy of midostaurin was demonstrated in a phase 2 trial involving a cohort of 20 patients diagnosed with FLT3-mutated AML or high-risk MDS. When administered as a standalone treatment, midostaurin exhibited noteworthy clinical activity, resulting in a substantial decrease in both blood and marrow blast counts.[55] Similar to sorafenib, most further studies evaluated midostaurin as part of combination therapy. The safety profile of midostaurin in conjunction with intensive chemotherapy was evaluated in a phase 1b trial involving 40 newly diagnosed patients below the age of 60, of whom 13 exhibited FLT3 mutations. The trial encompassed three distinct dosing schedules for midostaurin, and the results demonstrated a favorable safety profile. Importantly, midostaurin achieved a complete response in 92% of patients with FLT3 mutations, while maintaining an acceptable level of safety.[56]

Based on these data, it was evaluated in a phase 3 trial (RATIFY) that randomized 717 patients with FLT3 mutation at diagnosis to receive intensive chemotherapy alone or with midostaurin.[57] Initial rate of CR was similar with addition of midostaurin (58 vs. 53.5%) with median time to CR of 35 days. After a median follow-up of 59 months, OS was higher in the midostaurin group (74 vs. 25.6 months) with a 4-year OS of 51 versus 44%. However, several concerns were identified with this trial, which warrant further consideration.[58] For instance, the median age of patients with FLT3 mutations in this trial was much younger compared with published data and the study population was unusually enriched for FLT3-TKD mutations (22% compared with 5–6% in general). Patients with FLT3-TKD mutations, which do not result in worse prognosis compared with wild type FLT3, also

experienced significant clinical benefit from midostaurin. This finding supports the approval of midostaurin by the FDA in 2017 for newly diagnosed patients with FLT3-mutated AML, as it demonstrates the efficacy of the treatment across different FLT3 mutation subtypes.

It is essential to remember that midostaurin has no significant activity in patients with relapsed/refractory AML with preclinical studies only documenting "blast reduction" with no durable response.[59] Ongoing studies are currently assessing the efficacy of midostaurin in combination with gemtuzumab (NCT03900949, NCT04385290) and CPX-351 (NCT04982354) as part of the treatment regimen for newly diagnosed patients. These trials aim to further explore the potential benefits of incorporating midostaurin into combination therapies and expand our understanding of its effectiveness in different treatment approaches.

Concomitant use of posaconazole or voriconazole is associated with a significant rise in downstream metabolites and a 1.4-fold rise in drug exposure.[60] However, no clear effect on excessive toxicity has been observed, except a possible correlation with pulmonary toxicity initially noted in the RATIFY trial. In this trial, no dose reduction was specified, and a subsequent analysis observed that a higher-dose intensity was associated with higher clinical benefit without any increase in toxicity.[61] Thus, the current recommendation is to continue the drug at full dose along with azoles while closely watching for pulmonary complications to achieve maximal efficacy.[62]

Second-Generation FLT3 Inhibitors

Nondurability of clinical response and limited single-agent activity are important limitations of first-generation FLT3 inhibitors. Use of FLT3 inhibitors is also fraught with development of resistance mediated by secondary mutations in either FLT3-TKD or other related genes including *NRAS* and *AXL*, which allow a proliferative signal even in the presence of FLT3 inhibitors.[63] Second-generation FLT3 inhibitors were developed with an intention to overcome these limitations and provide better efficacy as monotherapy.

Quizartinib

Quizartinib (AC-220) was the first compound selectively designed to inhibit mutant FLT3-ITD with high potency and specificity, intended to overcome limitations of first-generation drugs.[64] Quizartinib underwent its initial evaluation in a phase I trial that enrolled 76 patients with relapsed AML who had experienced treatment failure following a median of three prior therapies, irrespective of their FLT3 mutation status. The primary objective of the trial was to assess the safety and tolerability of quizartinib in this specific patient population. The study aimed to gather preliminary data on the efficacy and potential therapeutic benefits of quizartinib as a treatment option for relapsed AML patients who had exhausted multiple prior therapies. ORR was 30%, with higher responses in the FLT3-ITD-mutated subset, with a median OS of 14 weeks. The most common dose-limiting serious adverse event was QT prolongation, noted in 12% of the population.[65]

The efficacy of quizartinib was subsequently evaluated in a phase 2 trial, specifically as a monotherapy, in a cohort of 333 patients with relapsed or refractory AML.[66] The study group was divided into two cohorts, first >60 years who progressed within 1 year of first-line therapy and second >18 years of age who received at least one salvage after progression. The rate of composite CR (CRc) in patients with FLT3 mutations in the first cohort was 56% and in the second was 46%. QTc prolongation was noted in 10% of patients.

The efficacy of quizartinib was assessed in a phase 3 trial known as QUANTUM-R, which specifically targeted patients with relapsed or refractory AML harboring FLT3-ITD mutations. In this trial, a total of 367 patients were randomly assigned to receive either quizartinib alone or salvage chemotherapy, with a ratio of 2:1.[67] The rate of CRc in the quizartinib group was 48% and chemotherapy group was 27%. Median time to first CRc was 4.9 weeks for quizartinib. After a median follow-up of 23.5 months (interquartile range: 15–32), median OS was higher with quizartinib (6.2 vs. 4.7 months, $p = 0.02$). Grade 3 QTc prolongation was present in 4% of patients in the quizartinib arm. Although this survival advantage may not be clinically significant, this trial demonstrated the feasibility of monotherapy with an oral drug in the relapsed/refractory setting.

Recently, data on front-line use of quizartinib was presented at the EHA 2022 meeting (Quantum-First study, EHA Abstract Erba H. 356965). A total of 539 patients were initiated on standard intensive chemotherapy and randomized to additionally receive quizartinib or placebo. Initial CR rates were similar (71 vs. 64%), although there was an increased risk of neutropenia with quizartinib. After a median follow-up of 39.2 months, OS was longer in the quizartinib arm (31.9 vs. 15 months). After censoring for hematopoietic stem cell transplantation, a trend to longer OS with quizartinib was observed (HR = 0.752; 95% CI = 0.56–1.008). These data led to accelerated regulatory approval of quizartinib as first-line therapy for newly diagnosed patients with FLT3-ITD mutations. Further studies of quizartinib in combination with idarubicin/cytarabine and cladribine (NCT04047641) and with azacytidine/venetoclax (NCT04687761) are currently underway.

Quizartinib is also metabolized by hepatic enzymes, and a 2-fold rise in maximal concentration and AUC is noted on concomitant use of azoles (except fluconazole).[68] A dose-dependent increase in the risk of QTc prolongation is noted, and dose reduction is recommended when using with concomitant strong CYP3A4 inhibitors such as posaconazole and voriconazole.[69]

Gilteritinib

Gilteritinib, a small molecule inhibitor of FLT3 and multiple kinases (FLT3-ITD, FLT3-TKD, c-Kit, ALK, and AXL), exhibits potent and long-lasting inhibitory effects, particularly against FLT3-ITD. Its inhibitory activity surpasses that of first-generation inhibitors, suggesting superior efficacy.[70] Inhibition of AXL and FLT3-TKD is clinically relevant due to their role in mediating secondary resistance to FLT3 inhibitor therapy.[71]

Safety and dosing of gilteritinib was established in a phase 1/2 study including 252 patients with relapsed/refractory AML. More than 90% inhibition of FLT3 signaling was observed with an ORR of 40%.[72] The most common toxicity was diarrhea and elevated liver enzymes. Further follow-up of these data indicated an ORR of 49% in patients with mutated FLT3. Patients who received a daily dose of >80 mg exhibited a median response duration of 20 weeks, accompanied by a median OS of 31 weeks.[73]

The promising efficacy observed as a single agent prompted the initiation of the phase 3 ADMIRAL trial. This trial involved the randomization of 371 patients with relapsed/refractory AML to receive either gilteritinib alone or salvage chemotherapy.[74] FLT3-ITD mutations were present in 88.4% of the overall cohort. CRc rate with gilteritinib was 54.3% compared with 21% with salvage chemotherapy (HR = 32.5; 95% CI = 22.3–44). Median OS with gilteritinib was 9.3 versus 5.6 months (HR for death = 0.64; 95% CI = 0.49–0.83). A higher proportion of patients received an allogeneic transplant in the gilteritinib arm (25 vs. 15%), but a survival advantage was maintained after censoring at the time of transplant. Importantly, equivalent efficacy was also maintained in patients with a FLT3-TKD mutation.

Long-term data from this trial were recently published in June 2022 with a median follow-up period of 37 months. As most relapses occurred in the first 18 months, OS at the end of follow-up was similar to data from the ADMIRAL trial. Two-year survival probability was higher with gilteritinib (20.6 vs. 14.2%). Serious adverse events were noted in 20.3% of patients receiving gilteritinib, the most common being elevated liver enzymes followed by cardiac events.[75] Although this study highlighted maximal clinical benefit for patients with FLT3-ITD high allelic ratio, a uniform benefit irrespective of FLT3-ITD allelic ratio and presence of comutations was confirmed in a subsequent analysis.[76] Based on these data, gilteritinib received regulatory approval for patients with relapsed/refractory AML with FLT3 mutations.

Gilteritinib was also evaluated recently in newly diagnosed patients with mutated FLT3 in a phase 3 trial (LACEWING study) in which 123 patients were randomized 1:1:1 to receive azacytidine alone, gilteritinib alone or both in combination.[77] Despite higher response rates (58.1 vs. 26.5%) and similar toxicity, no OS benefit was observed with combination therapy and the study was prematurely terminated.

Notable ongoing studies include gilteritinib in combination with venetoclax and azacytidine for newly diagnosed patients (NCT05520567), a head to head comparison with midostaurin (NCT04027309) and in combination with a Syk inhibitor lanraplenib for relapsed disease (NCT05028751).

Gilteritinib is also metabolized by the CYP3A4 enzyme system, and an increased AUC is observed when used concomitantly with azoles.[78] However, no dose reduction is currently recommended as no increase in clinical toxicity has been observed.[33]

Crenolanib

Crenolanib is a quinolone derivative initially developed as a PDGFR-α/β inhibitor targeting various solid tumors.[79] It's potential antileukemic properties were observed in vitro using a xenograft mouse model in 2013 with documentation of significant FLT3-ITD inhibition. Importantly, it was active against several FLT3-TKD (except F691L) mutations, which confer resistance to FLT3 inhibitor therapy, indicating a role in pretreated patients.[80,81]

Crenolanib was evaluated in a phase 2 study including 38 patients following a median of 3.5 prior lines of therapy, of which 13 were tyrosine kinase inhibitor (TKI) naïve and 21 had received previous TKI.[82] Among TKI-naïve patients, CRi + multiple layers file sharing system (MLFS) of 31% was observed, compared with 5% of those who had received previous TKI. Patients with CRi/MLFS had higher EFS (median: 22 vs. 8 weeks, $p = 0.003$) and OS (55 vs. 15 weeks, $p = 0.166$) with acceptable toxicity.

Efficacy in relapsed/refractory disease in combination with azacytidine or salvage chemotherapy was published in 2018 in a phase 2 study enrolling 28 patients, of which 20 received crenolanib with intensive chemotherapy and eight with azacytidine. ORR was 46%, with four patients achieving MRD negativity. Median OS was 4.7 months (range, 0.4–27 months) with no significant grade 3/4 adverse events.[83] Both of the aforementioned studies demonstrated the efficacy of crenolanib in relapsed/refractory AML. Intriguingly, among the patients who experienced disease progression while on crenolanib, resistance to treatment was observed to be driven by non-FLT3-dependent mechanisms, such as the emergence of secondary mutations in NRAS and IDH2.[84]

Crenolanib is recently being evaluated in newly diagnosed patients in combination with standard therapy. In a phase 2 study, 29 newly diagnosed FLT3-mutated patients were treated with intensive chemotherapy in combination with crenolanib and demonstrated MRD negativity in 80% of patients at the end of induction.[85] Long-term results of the trial were presented in the 2022 ASCO meeting and included data from 44 patients. With a median follow-up of 45 months, median OS was not reached and median EFS was 45 months.[86] Ongoing phase III trials include the comparison of crenolanib with midostaurin as a follow-up therapy after initial treatment (NCT03258931) and the evaluation of crenolanib in combination with intensive chemotherapy for relapsed/refractory patients (NCT03250338).

►**Tables 1** and **2** provide a summary of key trial results and important characteristics of the mentioned drugs, respectively, specifically focusing on drug administration

A Primer on Resistance to Targeted Oral Agents

With accumulating data on disease progression on targeted oral agents, several molecular mechanisms of resistance have emerged. In case of IDH1 inhibitors, both primary and secondary resistance to therapy may be noted.[87] Occurrence of oncogenic comutations in *DNMT3A*, *NPM1*, *ASXL1*, *SRSF2*, and *NRAS* and receptor tyrosine kinase pathway are associated with primary resistance to IDH1 inhibitors. Secondary resistance is mediated by either the emergence of new IDH2 mutations or alternate site IDH1 mutations (the

Table 1 Key evidence for FLT3 and IDH1/2 inhibitors showing clinical efficacy

Drug	Key study showing efficacy	*N*	Type	Clinical setting	Clinical use	Major finding	Regulatory approval received
Sorafenib	SORAML	276	Phase 2	Newly diagnosed AML	Combination with IC	Higher EFS (21 vs. 9 mo), similar CR and OS	No
Midostaurin	RATIFY	717	Phase 3 RCT	Newly diagnosed AML with FLT3-ITD	Combination with IC	Median OS 74 vs. 25 mo	Yes
Quizartinib	Quantum-FIRST	539	Phase 3 RCT	Newly diagnosed AML with FLT3-ITD	Combination with IC	Median OS 31 vs. 15 mo	Yes
Gilteritinib	ADMIRAL	247	Phase 3 RCT	Relapsed/refractory AML with IDH1 mutations	Monotherapy vs. salvage chemotherapy	Median OS 9.3 vs. 5.6 mo	Yes
Crenolanib	Wang et al, 2022[77]	44	Phase 2	Newly diagnosed AML with FLT3-mutated	Combination with IC	Median OS NR, median EFS 45 mo	No
Ivosidenib	AGILE	146	Phase 3 RCT	Newly diagnosed AML with IDH1 mutation	Combination with azacytidine	Median OS 24 vs. 7.9 mo	Yes
Enasidenib	IDHentify	319	Phase 3 RCT	Relapsed/refractory AML with IDH2 mutations	Monotherapy	Higher ORR (41 vs. 11%) and CR (26 vs. 3%), similar OS	Yes
Olutasidenib	–	153	Phase 2	Relapsed/refractory AML with IDH1 mutations	Monotherapy	ORR 48%, CR + CRi 35%, median OS 11.7 mo	Yes

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete count recovery; EFS, event-free survival; FLT3, FMS like tyrosine kinase 3; IC, intensive chemotherapy; IDH, isocitrate dehydrogenase; NR, not reported; ORR, overall response rate; OS, overall survival; RCT, randomized controlled trial.

Table 2 Salient details of clinical use of FLT3 and IDH1/2 inhibitors in acute myeloid leukemia

Drug name	Common dose used	Monotherapy/ combination	Important nonhematologic toxicities
Sorafenib	400 mg twice a day on D10 to 19 of induction	Combination with IC	Diarrhea (10% with Gd 3) and hand foot syndrome (7% with Grade 3)
Midostaurin	50 mg twice a day from D8 to D21 of induction	Combination with IC	Anemia, thrombocytopenia, skin rash/desquamation (14%)
Quizartinib	40 mg once a day from D8 to D21 of induction	Combination with IC	Neutropenia, QT prolongation (2.3% Grade 3)
Gilteritinib	120 mg once a day	Monotherapy	Febrile neutropenia, thrombocytopenia
Crenolanib	100 mg TID from D8 of induction	Combination with IC	Diarrhea (18% with Gd 3)
Ivosidenib	500 mg once a day	Combination with IC	Differentiation syndrome (14%)
Enasidenib	100 mg once a day	Monotherapy	Differentiation syndrome (13%), hyperbilirubinemia (26%)

Abbreviations: FLT3, FMS like tyrosine kinase 3; Gd, grade; IC, intensive chemotherapy; IDH, isocitrate dehydrogenase; TID, three times a day.

most common, R132-S280F), which restore intracellular concentrations of 2-hydroxyglutarate (2-HG).[88] Similarly, acquired transmutations in IDH2 restore 2-HG levels leading to clinical resistance to enasidenib.[89] These mutations are present in active enzyme sites (including R132 in IDH1 and R140/R172 in IDH2) and significantly increase the IC50 required for enzyme inhibition, leading to resistance to therapeutically achieved concentrations.[87]

Secondary IDH1 mutations can be overcome using newer IDH1 inhibitors, including IDH224, FT-2102, and DS1001B, which strongly bind to the mutated enzyme despite secondary mutations. This provides a potential to shift to alternate IDH1 inhibitors after failure of first-line therapy.[90]

Similarly, primary resistance to FLT3 inhibitors is known to be mediated by the site of FLT3-ITD mutations, each of which confer differing sensitivities to enzyme inhibition. Resistance is also mediated by the tumor microenvironment, where FLT3-mutated leukemia stem cells are protected and high CYP3A4 activity reduces local drug exposure.[91,92] Secondary resistance is mediated by either mutations in alternate signaling pathways or selection of clones with resistance conferring FLT3 mutations.[93] Similar mechanisms are active in case of quizartinib.[94] In contrast, resistance to gilteritinib and crenolanib is mediated by mutations in alternate genes, including *NRAS* and *IDH2*, implying the need for alternate approaches to overcome the same.[95]

Risk of Infections with Targeted Agents

It is vital to consider the risk of infections when using targeted agents, especially in the context of relapsed/refractory disease and in combination with other chemotherapeutic agents. The incidence of infectious complications associated with targeted agents can be estimated based on data from initial clinical trials. However, it is important to note that these complications may be reported variably as "infections," "febrile neutropenia," or "fever." The occurrence of these complications is contingent upon whether the drug is administered as monotherapy, in combination with chemotherapy, or in a posttransplant setting. ►**Table 3** provides a summary of these findings. Guidelines on the same were recently published by a multiple European societies in a joint venture.[96]

IDH1/2 Inhibitors

No specific increase in infectious complications have been noted with these agents. In initial trials of these agents as monotherapy, pulmonary infections were noted in 15 to 20% of patients, similar to other settings in AML. It must be noted that a higher risk of Clostridial infections was noted on combination with intensive chemotherapy in the initial phase 1 study with IDH1/2 inhibitors but has not been observed elsewhere.[30]

FLT3 Inhibitors

A recent clinical guideline assessed the risk of infections with midostaurin. The median incidence of febrile neutropenia was 35% and pneumonia was 9%, with sepsis ranging from 4 to 18%.[96] No excess risk of fungal or viral infections was observed. With quizartinib, the risk of sepsis as monotherapy was similar to salvage chemotherapy, with a slightly higher risk of pneumonia, warranting close monitoring.

Discussion

Intensive chemotherapy and stem cell transplantation may not be feasible (advanced age, reduced fitness, or logistic barriers) or effective (relapsed / refractory disease) in certain settings with AML.[8,97] In this setting, the combination of venetoclax with HMAs has significantly improved initial response rates and survival.[97,98] However, drug development for AML has lagged behind other hematologic malignancies and availability of targeted oral inhibitors represents the next important step forward in the treatment of AML.

Limitations

The limitations of this review lie in its narrative nature and lack of systematic literature selection and analysis,

Table 3 Overall incidence of infections in pivotal trials compared with placebo when used with intensive chemotherapy, low-dose therapy/monotherapy, or posttransplant maintenance

	Targeted agent combined with chemotherapy		Targeted agent used as monotherapy		Targeted agent in posttransplant setting	
	Infections in drug arm	Infections in control arm	Infections in drug arm	Infections in control arm	Infections in drug arm	Infections in control arm
	SORAML				SORMAIN	
Sorafenib	55%	48%	N/A	N/A	26.2%	23%
	RATIFY				NCT01477606	
Midostaurin	52%	50%	N/A	N/A	56%	–
	Quantum first		Quantum-R			
Quizartinib			31%	28%	–	–
	LACEWING		ADMIRAL			
Gilteritinib	35.6%	21.3%	46.7%	36.7%	–	–
	AGILE		NCT02074839			
Ivosidenib	28%	34%	18%	N/A	–	–
	AG221-AML-005		IDHENTIFY			
Enasidenib	37%	25%	2.5%	12.1%	–	–

Abbreviation: N/A, not applicable.

potentially introducing bias in the included studies. Without a predefined search strategy and inclusion criteria, certain studies may be overlooked, affecting the validity of findings.

Generalizability and Future Perspectives

The findings of our narrative review on FLT3 and IDH1/2 inhibitors in AML should be interpreted in the context of drug availability and regional differences. Although our review focused on both FLT3 and IDH1/2 inhibitors, it is important to note that only FLT3 inhibitors are currently available in India, while the availability of other inhibitors may vary worldwide. This limitation may affect the generalizability of our findings to regions where IDH1/2 inhibitors are commonly used in clinical practice. Additionally, variations in drug approval processes, treatment guidelines, and health care infrastructure across different countries can further influence the applicability of our findings. Therefore, caution should be exercised when extrapolating the results of our review to patient populations in regions where specific inhibitors are not available or where treatment practices differ. Further studies and collaborations across different regions are warranted to validate the efficacy and safety of IDH1/2 inhibitors in AML beyond the scope of our current review.

Conclusion

Drug therapy for AML is a field of active development, and several drugs with novel mechanisms including venetoclax, glasdegib, SYK, and menin inhibitors under evaluation.

The ultimate aim of targeted therapy for AML is the use of continuous low-toxicity regimens with a high response rate (similar to chronic myeloid leukemia) to improve survival for in this difficult to treat disease.

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