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Antifungal Prophylaxis in the Era of Targeted Chemotherapy for Acute Myelogenous Leukemia

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Abstract

Purpose of Review This review will provide an overview of the potential drug-drug interactions (DDIs) that may occur when using small-molecule kinase inhibitors (SMKIs) for the treatment of acute myeloid leukemia (AML) with triazole antifungals. We aim to discuss the management strategies for these interactions, including the assessment of invasive fungal disease (IFD) risks, alternative antifungal treatments, and dosage adjustments of SMKI therapy.

Recent Findings Recent advances in molecular and cell biology have led to the approval of several SMKIs for the treatment of AML. These targeted therapies, while more tolerable than traditional cytotoxic chemotherapy regimens, are metabolized via the cytochrome P450 3A4 pathway, making them susceptible to potential DDIs with triazole antifungals. Managing these interactions requires a tailored approach, taking into consideration the patient's specific IFD risks, treatment status, and comorbidities. While specific dosing guidance is available for using venetoclax or ivosidenib with triazole antifungals, recommendations for other SMKIs are less certain.

Summary The use of SMKIs in AML treatment has revolutionized patient care by providing more targeted and tolerable therapies. However, the potential for DDIs, particularly with triazole antifungals, necessitates careful management. Clinicians must carefully assess the specific IFD risks associated with SMKI therapies, evaluate the limitations of current and future antifungal treatments, and consider evidence supporting dosage adjustments when co-administering SMKIs with triazoles. Ongoing research in model-informed precision dosing and therapeutic drug monitoring holds promise for improving the safety and efficacy of managing drug interactions with SMKI therapy.

Keywords Targeted therapy · Antifungal prophylaxis · Acute myeloid leukemia · Invasive aspergillosis

Introduction

For over four decades, standard remission induction chemotherapy (RIC) for acute myeloid leukemia (AML) has been based on the administration of 7 days of cytarabine arabinoside (ARA-C) plus 3 days of anthracycline ("7 + 3") [1]. This regimen causes severe and prolonged cytopenia, requiring hospitalization and comprehensive supportive care to prevent infections, including antibacterial and antifungal prophylaxis [2]. For older and less-fit patients, the high treatment-related mortality of the 7 + 3 regimen often outweighs its curative benefits [3]. As a result, older patients with newly diagnosed AML are traditionally offered less intensive palliative chemotherapy with expected 5-year survival rates of < 10% [4].

Recent progress in molecular and cell biology has led to an improved understanding of the molecular drivers of leukemia, resulting in the development of molecular-targeted therapies [3]. Several of these therapies have already transformed the management of some subtypes of AML in both younger and older populations, allowing outpatient treatment with outcomes equivalent to or sometimes superior to those of the standard 7 + 3 regimens [3]. Notably, several observational studies have documented lower risks of invasive fungal disease with some targeted therapies, suggesting a possible reduced need for primary antifungal prophylaxis (PAP) [5–7].

A reassessment of the need for triazole prophylaxis is also driven by a wide spectrum of pharmacokinetic

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drug-drug interactions (DDIs) with targeted therapies. Recently approved treatments for AML are mostly small-molecule kinase inhibitors (SMKIs), which block cell-signaling pathways in malignant cells arising from somatic mutations [3]. Most of these inhibitors are metabolized via cytochrome P450 3A4/5 oxidative enzyme pathways in the liver, and are inhibited to varying degrees by triazole antifungals [8, 910

In this review, we examine the pros and cons of each strategy for the four most common SMKIs currently used in the treatment of AML: (1) anti-apoptotic B/cell lymphoma 2 (BCL-2) protein inhibitor venetoclax, (2) FMS-like tyrosine kinase 3 (FLT3) inhibitors (midostaurin and gilteritinib), (3) isocitrate dehydrogenase 1 and 2 (IDH1/2) inhibitors (ivosidenib and enasidenib), and (4) sonic hedgehog inhibitor (glasdegib). We summarized recent data concerning the risks of IFD with SMKIs used in AML treatment, the advantages and disadvantages of non-triazole-based prophylaxis, the safety of empiric dose adjustments for SMKIs, and the potential risks of using triazole with full-dose SMKI-targeted therapy.

Is Triazole Prophylaxis Necessary in Patients Receiving Targeted Chemotherapy Regimens?

Antimicrobial prophylaxis can be justified if an infection is (1) sufficiently serious such that it incurs significant morbidity and mortality even when diagnosed and treated early, (2) sufficiently common to justify universal prophylaxis (e.g., > 10% incidence as a rule of thumb), and (3) difficult to diagnose [11]. The first two criteria are widely accepted for IFDs during initial RIC therapy for AML [12]. Nucci and Anaissie [13] summarized individual patient risk for IFD during AML treatment into four categories:

1. Host fitness for standard chemotherapy (i.e., fit, unfit, or frail)
2. Leukemia resistance (high versus low probability of achieving complete remission (CR)) and current malignancy status
3. Anticipated treatment-related toxicities, such as neutropenia, mucositis, and steroid-induced immunosuppression
4. Patient exposure to opportunistic fungi

While the substitution of SMKIs for more cytotoxic 7 + 3-based regimens may lessen some treatment-related complications, such as mucositis, a substantial proportion of patients receiving these regimens are frail and continue to develop prolonged neutropenia. Therefore, the continued need for PAP in patients receiving targeted chemotherapy depends heavily on their clinical circumstances.

The need for primary antifungal prophylaxis in patient populations receiving newer targeted therapies has been examined in recent clinical practice guidelines from the European Conference on Infections in Leukaemia (ECIL) [14] and recommendations from the European Hematology Association (EHA) prepared in cooperation with the Cochrane Hematology Group [8••]. The EHA recommendations examined 19 relevant novel targeted agents that are currently approved or are in later stages of clinical trials, summarized the evidence, and provided recommendations. A summary of the key recommendations of this group for currently approved agents is provided in Table 1. PAP with posaconazole is recommended if patients receive targeted therapies as part of a standard intensive RIC regimen. During consolidation chemotherapy, the risk of IFD was considered lower unless the patient experienced persistent neutropenia or had a history of fungal infection [15]. In such cases, continuation of posaconazole prophylaxis is recommended when SMKIs are administered as part of maintenance or consolidation.

The inherent challenges of diagnosing fungal infections have long been used to support the practice of both prophylaxis and empiric antifungal therapy for fungal diseases in patients with hematological malignancies [12]. With the increasing availability of non-culture-based diagnostic tests, such as galactomannan and β-D-glucan, PCR testing for fungal nucleic acids, and timely access to high-resolution computed tomography (CT) imaging, some centers have transitioned from universal PAP to diagnostic-driven (preemptive) treatment approaches. A recent EORTC trial compared patients with AML randomized to a preemptive IFD management approach with fluconazole prophylaxis to empiric treatment with caspofungin after 96 h of fever with broad-spectrum antifungals [16]. On day 42, overall survival (OS) rates were similar between the two treatment groups (96.7% preemptive vs. 93.1% empiric), with a 50% reduction in the use of mold-active antifungals in patients randomized to the preemptive treatment arm. However, no randomized trials to date have compared primary antifungal prophylaxis with posaconazole versus a preemptive diagnostic-driven strategy for IFD in AML patients.

In allogeneic SCT recipients, a preemptive strategy approach of administering fluconazole prophylaxis with galactomannan monitoring was shown to be as safe and effective as voriconazole prophylaxis, both in terms of 6-month fungal-free survival (FFS) and relapse-free and overall survival [17]. However, in the cohort of patients transplanted for AML, voriconazole prophylaxis was associated with significantly fewer IFD cases (8.5% vs. 21%, $P = 0.04$), improved FFS (78% vs. 61%, $P = 0.04$), and a trend towards improved overall survival (81% vs. 72%,

Table 1 EHA guidelines on antifungal prophylaxis in adult AML patients treated with novel targeted therapies

Targeted therapy	Molecular target	Evidence of a therapeutic range for efficacy (reported mean/median $C_{min,ss}$ at standard doses)	Mechanism of immunosuppression risk	Impact on the risk of invasive fungal disease	Triazole prophylaxis recommended
BCL-2 inhibitor (venetoclax)	Selective inhibitor of anti-apoptotic protein BCL2	No proposed TDM target (520 ng/ml)	Neutropenia	Limited evidence, but overall risk is low, except in patients with prior allogeneic stem cell transplant, prolonged neutropenia, or when used for resistant/refractory AML	Conditional, but should be considered for patients with prolonged neutropenia Dosage adjustment required when given with triazole
FLT3 inhibitors (midostaurin, gilteritinib)	Inhibition of FMS-like tyrosine kinase 3	Yes, blood blast response No proposed TDM target: For midostaurin, 50 mg BID (467 ng/ml); 100 mg BID (919–1064 ng/ml) Exposures correlate with hepatotoxicity risk Gilteritinib proposed TDM target: $C_{ss,min} > 100$ ng/ml (456 ng/ml)	Neutropenia	Limited evidence, no studies to date suggesting increased risk	Triazole prophylaxis recommended when given as part of remission induction chemotherapy Individualized decisions when given as part of maintenance chemotherapy Patients must be monitored closely for toxicities due to expected drug interactions
IDH1/2 inhibitors (ivosidenib, enasidenib)	Isocitrate dehydrogenase 1/2 enzyme inhibitors	No proposed TDM target: AUC_{0-24}: 11,700 ng/ml/h	Neutropenia	Limited evidence, no studies to date suggesting increased risk	Conditional, but should be considered for patients with prolonged neutropenia
Sonic Hedgehog inhibitors (glasdegib)	Smoothened Hedgehog pathway	No proposed TDM target; exposures correlated with dysgeusia and QT prolongation (365 ng/ml)	Neutropenia	Limited evidence, no studies to date suggesting increased risk	Conditional, but could be considered for patients with prolonged neutropenia

These recommendations were made by Stemler et al. [8••]. Data on drug exposure and therapeutic range were obtained from Mueller-Schoell et al. [78••]

$P = 0.32$). Therefore, the equivalence of preemptive and prophylactic strategies for the highest-risk population is uncertain [18]. In the absence of more definitive data, diagnostic-driven strategies may be more feasible in patients receiving SMKIs during the consolidation or maintenance phase of chemotherapy, when neutropenia is generally shorter. Decisions regarding which strategy should be used are often highly individualized according to the clinical circumstances and diagnostic resources available. Importantly, preemptive strategies require access to non-culture-based tests and timely CT imaging [12], including when patients are in an outpatient setting where the bulk of SMKI therapy is administered. Point-of-care tests, such as the availability of simpler sensitive lateral-flow *Aspergillus* antigen assays, could facilitate IFD monitoring in outpatient settings [19].

Should the Patient Be Switched to Alternative Antifungal Prophylaxis Without CYP3A4/5 Interactions?

Echinocandins or liposomal amphotericin B (L-AMB) are often considered alternatives to triazoles in patients eligible for SMKIs or in clinical trial protocols that prohibit concurrent triazoles because of the risk of QT prolongation. Micafungin is the only echinocandin currently approved for prophylaxis of *Candida* infection in patients undergoing allogeneic hematopoietic stem cell transplantation or in those expected to have neutropenia (absolute neutrophil count < 500 cells/μL) for ≥ 10 days. Guidelines for the treatment of invasive aspergillosis do not recommend echinocandin monotherapy as a frontline treatment for invasive aspergillosis because of the available data suggesting poorer response rates for primary therapy of probable or proven invasive aspergillosis (IA) [20–22]. A recent open-label randomized trial comparing prophylaxis with caspofungin versus fluconazole in children and adolescents undergoing treatment for AML found a significantly lower cumulative incidence of proven or probable aspergillosis in patients randomized to the caspofungin arm (0.5% vs. 3%, $P = 0.04$) [23]. However, the rates of IA in the fluconazole arm were lower than those reported in previous adult studies that compared posaconazole suspension to fluconazole/itraconazole (1% vs. 7%, $P = 0.04$) [24]. Therefore, despite the perceived safety benefits of avoiding CYP P450 inhibition with echinocandin, the equivalence of echinocandin versus standard posaconazole prophylaxis remains debatable.

Echinocandin prophylaxis may also be associated with greater breakthrough infections caused by rare yeast [25, 26] and intrinsically resistant molds such as *Fusarium* spp. and Mucorales compared to mold-active triazoles. In centers or regions where these infections are more common, careful consideration should be given to the early diagnosis of these less common breakthrough infections in patients receiving echinocandin prophylaxis given their propensity for rapid dissemination.

Intravenous L-AMB is occasionally used off-label for prophylaxis, either intravenously or in aerosolized form, delivered through a nebulizer [27]. The optimal dosing approach for L-AMB prophylaxis in AML patients undergoing RIC remains unclear. L-AMB prophylaxis has occasionally been recommended for adult patients with acute lymphoblastic leukemia (ALL), where the use of intensive chemotherapy regimens containing vinca alkaloids that are metabolized through CYP3A4 precludes the use of triazole antifungals because of the risk of neurotoxicity and peripheral neuropathy that occurs with elevated vinca alkaloid exposure [28]. Novel therapies for relapsed/refractory ALL, such as the bispecific T-cell engager therapy blinatumomab, the CD22-directed antibody drug conjugate inotuzumab, and CD19-targeted chimeric antigen receptor-modified T (CAR-T) cell therapies, are being evaluated as induction chemotherapy and may carry unique risks for the development of IFD [28]. Data on how these novel treatments affect the incidence and outcomes of IFD such as aspergillosis are limited.

Cornely et al. [29] performed a double-blind multicenter phase 3 study comparing twice-weekly prophylactic intravenous 5 mg/kg L-AMB or placebo during remission induction treatment. The rates of proven and probable IFD were similar between the L-AMB and placebo groups (7.9% vs. 11.7, $P = 0.24$), with similar mortality rates (7.2% vs. 6.8%). Hypokalemia (35.0% vs. 17.8%, $P < 0.001$) and increased creatinine (> 1.5 × baseline, 3.0% vs. 0%, $P < 0.001$) were more frequent in patients who received L-AMB prophylaxis. The lack of observed efficacy in ALL patients randomized to receive L-AMB relative to placebo may reflect ineffective intermittent L-AMB doses or possibly good outcomes in the placebo group with early diagnosis and treatment of IFD [29].

Echinocandins and liposomal amphotericin B must be administered intravenously, making them impractical for prolonged use in outpatient settings where most oral SMKIs are administered. Infrequent dosing of micafungin may be feasible, although its efficacy has not been evaluated in randomized trials [30]. Although less frequently administered higher doses of L-AMB (< 5 mg/kg/day) have been shown to be effective in combination with other antifungal agents for other fungal diseases [31], clinical data supporting this dosing approach as prophylaxis for mold infections are lacking [27].

Several new antifungal drug candidates currently in clinical trials have shown promise for the prevention or treatment of IFD in patients receiving SMKIs. An oral echinocandin-like triterpenoid recently approved for the treatment of vulvovaginal candidiasis, ibrexafungerp, is currently under investigation for the treatment of refractory fungal diseases and as a step-down therapy from intravenous echinocandins [32, 33].

Relatively little data are available regarding its efficacy in the treatment of invasive aspergillosis, and no current studies support its role in primary antifungal prophylaxis. Similarly, once weekly rezafungin, an intravenously administered anidulafungin analog, was reported to be non-inferior to daily treatment with IV caspofungin in a multicenter phase III trial of invasive candidiasis in non-neutropenic patients and was approved by the US FDA for the treatment of invasive candidiasis [34]. Currently, rezafungin is being investigated for the prevention of IFDs and *Pneumocystis jirovecii* pneumonia in patients undergoing allogeneic HST (Clinical Trials.gov, NCT04368559).

Other investigational antifungals reported to have less potent inhibitory potential against human CYP3A4/5 enzymes include fosmanogepix (manogepix), olorofim, and tetrazoles [35]. Fosmanogepix (manogepix) is a broad-spectrum antifungal that inhibits the conserved glycosylphosphatidylinositol (GPI)-anchored wall transfer protein (Gwt1) in fungi, which mediates crosslinking of mannoproteins to β-1,6-glucans. Available data suggest that it is not a potent inhibitor of CYP3A4 [36], although it is likely a substrate of CYP P450 enzymes, as murine infection models require the administration of the cytochrome P450 inhibitor 1-aminobenzotriazole (ABT) to mimic human pharmacokinetics. Olorofim is an orotomide antifungal that inhibits dihydroorotate dehydrogenase (DHODH) in the pyrimidine biosynthesis pathway of susceptible molds, but not in yeast, arresting nucleic acids, cell walls, and phospholipid synthesis [37]. It is a weak inhibitor of CYP3A4 and is metabolized by CYP3A4 enzymes. Olorofim must be administered with a secondary agent (e.g., fluconazole or echinocandin) to provide an adequate coverage of both yeast and molds, possibly expanding drug interaction risks. Finally, a new series of triazole analogs (tetrazoles) with enhanced potency, prolonged half-lives, and selectivity for fungal CYP51A have been reported in clinical trials (oteseconazole, quilseconazole, and VT-1598), which could theoretically have unique advantages for the prophylaxis or treatment of IFD in patients requiring SMKIs. However, the current developmental plan for tetrazoles involves recurrent VVC, endemic fungal infections, and cryptococcal meningitis [35].

Is an Empirical SMKI Dose Reduction Safe for Triazole Antifungals?

Product labeling for most SMKIs includes warnings regarding the concomitant use of potent CYP3A4/5 inhibitors, such as voriconazole and posaconazole. For some drugs, such as venetoclax, limited pharmacokinetic data are available to support empiric dose reductions for SMKIs when used in combination with moderate (fluconazole and isavuconazole) or strong (posaconazole and voriconazole) CYP3A4/5 inhibitors [38]. Current recommendations for the most common SMKIs used in AML treatment are discussed below.

Venetoclax

Venetoclax is a potent selective BCL-2 inhibitor approved for the treatment of chronic lymphocytic leukemia and AML. Over-expression of BCL-2 contributes to chemotherapy resistance and tolerance to cellular apoptosis [39]. Venetoclax, in combination with hypomethylating agents (HMAs), improves remission rates and prolongs overall survival in elderly patients with newly diagnosed AML [3]. In a phase I study of patients aged over 65 years [40], the most common adverse effects of combination therapy included febrile neutropenia (43%), leukopenia (31%), anemia (25%), thrombocytopenia (24%), neutropenia (17%), and pneumonia (13%). Infections of all grades occurred in three-fourths of the patients (45%, grades 3–4), with pneumonia (18%) being the most common. Most deaths in patients who received a combination of venetoclax and HMA were attributed to infection.

Agarwal et al. [38] examined the effect of posaconazole on the pharmacokinetic properties of venetoclax in 12 patients to determine the dose adjustments needed to manage this potential interaction. When adjusted for different doses and nonlinearity, posaconazole was estimated to increase venetoclax C_{max} and AUC_{0-24} by 7.1- and 8.8-fold, respectively, suggesting that posaconazole can be used as an antifungal prophylaxis after reducing the venetoclax dose by at least 75% to 100 mg daily. For moderate CYP3A4/5 inhibitors (fluconazole and isavuconazole), an initial 50% reduction in venetoclax dosage is recommended [41]. These dosing adjustments are included in venetoclax labeling, although the availability of only 10 mg, 50 mg, or 100 mg tablets can complicate dosing and increase the risk of medical errors and medication costs [42, 43]. Therefore, 100 mg is often used as a "one size fits all" adjusted dose for patients receiving posaconazole prophylaxis.

Prolonged cytopenia, bleeding, and infection are the major risks associated with the use of triazole antifungals such as posaconazole with venetoclax/HMA therapy [10••]. It is important to understand whether reduced doses of venetoclax in combination with posaconazole have similar safety and efficacy as when the drug is used at full doses without triazoles in older patients. Rausch et al. [43] reported that while the time to neutrophil recovery (ANC > 1000 cells/mm^3) and the number of infections were not significantly prolonged in 64 patients who received triazoles with dose-adjusted venetoclax plus hypomethylating agents for newly diagnosed AML, the median time to platelet recovery was prolonged in patients who received triazoles (28 days vs. 22 days, $P = 0.01$). No differences in bleeding events were observed according to the study design. The authors concluded that the combination of venetoclax 100 mg daily with either posaconazole or voriconazole resulted in a similar duration of

neutropenia and thrombocytopenia as the standard 400 mg dose administered without triazoles and was well tolerated [43]. Future pharmacokinetic analyses of patients receiving venetoclax and posaconazole may allow more precise dosing adjustments and improved safety.

FLT3 Inhibitors

Mutations in the FLT3 gene are the most common cytogenetic abnormalities observed in patients with AML and are present in up to one-third of newly diagnosed patients. Internal tandem duplication (FLT3-ITD) within the juxtamembrane domain is associated with poor prognosis, reduced survival rates, and increased risk of relapse [44]. In 2017, the US FDA approved the first drug, midostaurin, as part of remission induction chemotherapy for FLT-mutated AML. The second agent, gilteritinib, was approved in 2018 for the treatment of relapsed or refractory AML associated with FLT3 mutations. Both agents undergo extensive metabolism through CYP3A4, and recommendations are included to avoid concomitant treatment with potent CYP3A4 inhibitors such as voriconazole and posaconazole whenever possible. Unlike venetoclax, no empirical dosing adjustment recommendations have been established for midostaurin or gilteritinib when co-administered with potent CYP3A4 inhibitors [45].

In vitro and clinical studies have indicated that midostaurin and its two active metabolites, CGP52421 and CGP62221, are substrates, reversible and time-dependent inhibitors, and inducers of CYP3A4 [46–48]. Physiological-based pharmacokinetic models have predicted up to a tenfold increase in the midostaurin AUC (90% CI 7.4–14.5) when the drug is administered with strong CYP3A4 inhibitors such as ketoconazole and itraconazole as compared to placebo [49]. Early clinical trials also reported fatal pulmonary events in patients who developed excessive midostaurin exposure while receiving concomitant triazole antifungals [47].

The phase III RATIFY trial randomized newly diagnosed AML patients with either midostaurin or placebo with 3 + 7 (daunorubicin with cytarabine) induction and high-dose cytarabine consolidation therapy (up to four consolidations), followed by 12 months of maintenance with either midostaurin or placebo [50]. In this trial, concomitant strong CYP3A4 inhibitors were allowed with posaconazole and voriconazole, which are the most common inhibitors administered during the initial remission induction phase. Among the patients who received a concomitant strong CYP3A4 inhibitor in the trial (60.8%), midostaurin exposures increased 1.44-fold and shortened the time to grade 3/4 toxicities (36 days vs. 41 days, respectively; $P = 0.012$) [51]. QT interval prolongation (< 480 ms) has been reported in 10.1% of patients receiving standard doses of FLT3 inhibitors [52]. Notably, a higher-intensity midostaurin dose was associated with benefits in event-free survival (EFS) and OS, and the presence of CYP3A4 inhibitors did not have a significant impact on efficacy outcomes. The investigators concluded that the concomitant use of strong CYP3A4 inhibitors was not a contraindication to midostaurin therapy, but that clinicians should be vigilant in monitoring midostaurin-related toxicities [51].

Schlenk et al. [53] performed a prospective phase II study of midostaurin that included patients of the age range 61–70 years and included a strategy that reduced the midostaurin dose by 50% if patients were administered strong CYP3A4 inhibitors, although the dose reduction was abandoned at later stages in the trial. Interestingly, mortality among patients aged 61–70 years was substantially lower than that among those treated after the midostaurin protocol amendment (2.4% vs. 15.7%). This finding was hypothesized to be a result of reduced midostaurin toxicity [53]. However, given the potential risks of reduced OS and EFS with midostaurin dose reduction, empirical dosage adjustments with CYP3A4 may not be advisable in the absence of toxicity and without monitoring midostaurin serum drug concentrations or FLT3 biomarkers (e.g., FLT3 plasma inhibitory activity) [54]. However, biomarker monitoring is not routinely used in most centers and will require validation for dosage individualization in addition to more widely used approaches for monitoring minimal AML residual disease by molecular methods or flow cytometry.

Gilteritinib is a selective FLT3 inhibitor that is a substrate of both P-glycoprotein (P-gp) and CYP34. Unlike midostaurin, gilteritinib is not biotransformed into its active metabolites [55]. The co-administration of gilteritinib with itraconazole and low-dose fluconazole (400 mg and 200 mg daily) resulted in a twofold increase and a 1.4-fold increase in gilteritinib exposure, respectively, in healthy subjects [56]. However, no increase in reported adverse effects was evident among the cohort of resistant/refractory AML patients undergoing gilteritinib treatment while receiving moderate (fluconazole) or strong (voriconazole and posaconazole) CYP3A4 inhibitors [54]. Consequently, gilteritinib dose reduction is generally not recommended, except in patients who experience QTc prolongation of > 500 ms, where the recommendation is to hold doses and restart at a 50% lower dose once the QTc interval falls below 480 ms. In the composite safety analysis, only 5% of patients experienced QTc prolongation > 480 ms and 2% experienced prolongation > 500 ms [57].

IDH1/2 Inhibitors

Ivosidenib and enasidenib are oral selective inhibitors of IDH1 and IDH2, which target abnormal metabolism in leukemic blast cells. Both agents are approved for the treatment of newly diagnosed AML in adults aged 75 years or

older, in those with comorbidities that preclude the use of intensive induction chemotherapy, and in patients with resistant/refractory AML associated with documented IDH mutations. Ivosidenib is metabolized in the liver by CYP3A4 [58], and its co-administration with triazoles has been associated with significant increases in AUC, including fluconazole (69–73%), voriconazole (90%) [59, 60], and posaconazole (169%) [61]. Current prescribing information recommends a dose reduction from 500 to 250 mg/day when strong CYP3A4 inhibitors, such as posaconazole, are co-administered (Table 2).

Enasidenib is uniquely metabolized by multiple cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) as well as uridine diphosphate (UDP)-glucuronosyltransferase (UGT) to inactive metabolites [62]. Because of this multienzyme metabolic profile, no relevant drug interactions with moderate or strong CYP3A4 inhibitors have been reported in patients [62].

Glasdegib

Glasdegib is a potent and selective inhibitor of smoothened Hedgehog, a transmembrane protein involved in signaling pathways that enhance tumorigenesis and resistance to chemotherapy. In 2018, glasdegib (100 mg once daily in combination with low-dose ARA-C) was approved for the treatment of newly diagnosed AML patients aged > 75 years with comorbidities that preclude intensive remission induction chemotherapy.

Glasdegib is metabolized primarily through CYP3A4 with minor contributions of CYP2C8 and UGT1A9 [63]. In a healthy volunteer study, a 2.4-fold increase in the AUC of glasdegib was reported when the drug was administered with the potent CYP3A4 inhibitor ketoconazole [64–66]. As a result, co-administration of glasdegib with potent CYP3A4 inhibitors is not recommended [63]. If glasdegib is co-administered with triazoles, patients should be carefully monitored for QTc prolongation; however, no dosage adjustments have been proposed [63].

Should Isavuconazole Be the Preferred Triazole in Patients Receiving SMKIs?

Although not currently approved for prophylaxis, isavuconazole (isavuconazonium sulfate) has unique characteristics compared to other broad-spectrum triazoles, which may make it safer to use in combination with SMKI therapy for AML. Isavuconazole has more predictable oral bioavailability and less intra-individual variability in drug clearance than posaconazole and voriconazole and is a less potent inhibitor of CYP3A4/5 enzymes, resulting in a lesser impact on the clearance of SMKIs [67–69]. Other triazoles prolong cardiac QT waveforms by inhibiting the human ether-a-go-go (hERG) channel, increasing the risk of ventricular arrhythmias such as Torsades des Pointes [70]. In contrast, isavuconazole is a dose-dependent inhibitor of hCAv1.2 L-type Ca^{2+} channels that causes dose-dependent QT shortening [71]. Compared to voriconazole and posaconazole, isavuconazole treatment

Table 2 Summary of triazole drug interactions and currently recommended empiric dosage adjustment recommendations for SMKIs

	Venetoclax	Midostraurin	Gilteritinib	Ivosidenib	Enasidenib	Glasdegib
Approved dose	400–600 mg QD	50 mg BID	120 mg QD	500 mg QD	100 mg QD	100 mg QD
Strong CYP3A4 inhibitor[1]	Dose adjustment (75% reduction)	Consider alternative antifungal or careful monitoring; some have advocated a 50% dose reduction (25 mg BID) and careful monitoring [53]	Consider alternative antifungal or careful monitoring	Dose adjustment (50% reduction)	No action required	Consider alternative antifungal
Moderate CYP3A4 inhibitor[2]	Dose adjustment (50% reduction)	No action required	No action required	Alternative drug or careful monitoring	No action required	No action required
Strong CYP3A4 inducers[3]	Avoid	Avoid	Avoid	Avoid	No action required	Avoid

Recommendations from the manufacturer's summary of product characteristics and from Megías-Vericat et al. [61]

[1]Strong inhibitors: voriconazole, posaconazole, and itraconazole

[2]Moderate inhibitors: fluconazole and isavuconazole

[3]Strong CYP3A4 inducer: rifampin

is also associated with lower rates of cutaneous, CNS, visual, and hepatic adverse effects, which overlap with common treatment limiting SMKI toxicities (Fig. 1) [72].

Bose et al. [42] evaluated the potential role of isavuconazole prophylaxis in a cohort of 65 patients undergoing RIC for AML/MDS. Nearly half (49%) of the enrolled patients received oral targeted leukemia treatment (venetoclax and FLT3 inhibitors). Proven or probable invasive fungal infections (IFIs) were detected in 6% and 12% of patients, respectively, but none of the breakthrough infections developed in the setting of the subtherapeutic (< 1 μg/ml) drug exposures (day 8, median 3.37 μg/ml, range 1.18–7.65). Isavuconazole was well tolerated, with only two patients (3%) developing grade 1 transaminitis, possibly related to isavuconazole, and one patient (1.5%) developed isolated hyperbilirubinemia. This is in contrast to a previous experience with posaconazole in the same institution, where grade III/IV liver injury (primarily hyperbilirubinemia) was observed in 9% of patients receiving a tablet or IV formulation of posaconazole [73]. Despite including older patients, treatment-related mortality rates were low (< 8%) and isavuconazole had no apparent effect on CR rates compared with patients previously treated with venetoclax or FLT3 inhibitors [42].

Several centers have reported higher rates of breakthrough IFIs in patients receiving isavuconazole prophylaxis than in those receiving posaconazole prophylaxis [74, 75], although this finding has not been confirmed in all centers [76]. Rausch et al. [77••] examined the incidence and characteristics of breakthrough IFIs (bIFIs) in 277 adult patients with newly diagnosed AML undergoing RIC with high- or low-intensity venetoclax regimens. Proven or probable bIFI was observed in 11 (4%) patients. The incidence of bIFI was 2.9% and 4.8% for posaconazole and voriconazole, respectively, and 5.7% for voriconazole ($P = 0.55$). The main risk factors for bIFI are prolonged neutropenia and failure to achieve CR with RIC. Notably, the *lower-intensity* venetoclax regimens were not associated with a lower risk of bIFI. The rates of bIFI and toxicities were comparable between voriconazole, posaconazole, and isavuconazole, suggesting that all three triazoles could be reasonable choices for primary antifungal prophylaxis [77••]. These findings require confirmation in larger observational case series or clinical trials.

What Is the Potential Role of Therapeutic Drug Monitoring?

Despite the characterization of many SMKIs as precision therapies, current dosing recommendations for these agents are far from precise. Generally, a "one size" fits all dosing and dosing adjustments are recommended when administered in combination with CYP3A4 inhibitors, even though most of the SMKIs exhibit considerable pharmacokinetic variability and a narrow therapeutic range [78••]. Therapeutic drug monitoring (TDM) is the most direct method for detecting altered drug exposure in patients and can theoretically improve the accuracy and safety of SMKI dose adjustments [79•].

Two other criteria must be met for TDM to be clinically useful. First, the drug must have a definite and relatively narrow

Fig. 1 Non-infection-related adverse effects are most frequently reported with targeted therapy for acute myelogenous leukemia. The data were summarized by Wang and Baron [10••]. Figure prepared using the tool available at www.biorender.com

therapeutic range such that variability in drug levels would potentially jeopardize the anti-leukemic effects or the probability of developing treatment-limiting adverse effects. In a scoping review of new targeted therapies, Mueller-Schoell and colleagues [78••] identified a sufficient evidence of an established therapeutic range for FLT3 inhibitors gilteritinib and midostraurin, but there were insufficient data to recommend a therapeutic range for IDH1/2 inhibitors or venetoclax (summarized in Table 1). In the absence of a defined therapeutic range, the authors and regulatory agencies have suggested that population mean and median trough concentrations (C_{min}) could be used as proxy targets, as experience has shown that this target often encompasses 85% of target exposures once drugs have established therapeutic ranges [78••]. The second requirement is the availability of a sensitive and timely assay for serum drug levels of SMKI.

In the setting of drug interactions, TDM results can be used to adjust doses more accurately based on recommendations in product labeling, dosing equations, or nomograms. However, these dosing adjustment methods are less precise if serum drug level monitoring is not performed according to the schedule or if the patient is not represented by the population on which the label or dosing algorithm was developed [79•]. Model-informed precision dosing (MIPD) approaches use population (nonlinear mixed effects) pharmacokinetic models to predict drug exposures/dosing regimens based on patient characteristics that have a higher probability of being safe and effective. The model can then be further "fine-tuned" using several TDM measurements and Bayesian inference to establish patient-specific pharmacokinetics in the setting of drug interactions to simulate and predict dosing adjustments [79•]. In theory, MIPD represents a more efficient and safe approach towards dosage adjustment with drug interactions than currently trial-and-error approaches. Increasingly, these models are being developed for more user-friendly web and smartphone-based applications for point-of-care use [79•]. However, certification of these pharmacological tools for TDM is subject to regulatory approval and is still not widely available [80].

Summary

We have entered a transformative in the treatment of hematological malignancies with targeted therapies, immunotherapy, and precision medicine offering incredible potential for effective treatment with less toxicity and better outcomes. Supportive care for patients will need to undergo similar transformation to ensure patients optimally benefit from these medical advances and to prevent excess morbidity from infections, drug toxicity, and drug interactions. Similarly, more individualized approaches to supportive care in terms of risk assessment, risk management, and antifungal dosing/monitoring will be required to achieve the optimal benefit from newer chemotherapies as fungal infections will become more heterogeneous, and increasingly managed in the outpatient setting in a growing population of chronically immunosuppressed patients living with leukemia.

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Declarations

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- • Of importance
- •• Of major importance

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