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

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Keywords

Competing interests

Abstract

150-250 words

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia diagnosed in adults with a historically poor prognosis. Remission-induction chemotherapy used for the treatment of AML causes prolonged and profound neutropenia, placing patients at high risk for mold infections such as invasive aspergillosis (IA)[1]. In addition to their considerable morbidity and mortality, IA jeopardizes the intensity and timing of subsequent consolidation chemotherapy [2,3] or stem cell transplantation [4] increasing the risk of leukemia relapse. As a result, primary mold-active antifungal prophylaxis, most commonly with posaconazole, is recommended during remission-induction chemotherapy to prevent fungal infections [5]. This approach is supported by a pivotal randomized clinical trial that demonstrated a significant reduction in both fungal infections and all-cause mortality in patients undergoing AML treatment with prolonged neutropenia who received posaconazole prophylaxis [6].

Over the last two decades, high resolution cytogenetic analysis and next-generation sequencing have better defined the molecular drivers of leukemogenesis and disease progression leading to and explosion of novel therapies for AML [7]. Many of these novel therapies are represented by small molecular kinase inhibitors that target aberrant signalling in leukemic cells that arise from somatic mutations. Since 2017, the U.S. Food and Drug Administration has approved X SMKIs for the treatment of AML, which are now incorporated at various treatment phases for most subtypes of AML, particularly in older adults who cannot tolerate intensive cytoreductive chemotherapy [8].

Despite the promise of these novel therapies, their clinical use is complicated by pharmacokinetic drug-drug interactions with agents that block their metabolic clearance through CYP3A4/5 pathways [9] Mould-active triazole antifungals such as posaconazole, in particular, alter the clearance of most SMKIs and increase the risk of potential serious and life-threatening toxicities [10]. Therefore clinicians are faced with the prospect of (i) potentially stopping triazole antifungal prophylaxis to avoid drug interactions with the SMKI; (ii) switching to an alternative antifungal without CYP3A4/5 interactions; (iii) empirically reducing the dose of the SMKI to account for the effect of triazole CYP3A4/5 inhibition; or (iv) continuing both the SMKI and triazole at full dose and monitoring the patient carefully for toxicity. Each of the choices are associated with risks to the patient. Therefore, the choice of which strategy to follow may vary from one patient to the next depending on the treatment setting and available resources for diagnostic testing and therapeutic drug monitoring.

In this review, we address these four questions for the three most common class of prescribed SMKIs-venetoclax, FLT3 inhibitors (midostaurin, gilteritinib, quizartinib) and IDH inhibitors (ivosidenib, enasidenib). We will specifically focus on recent data examining what is known about the potential risks for IFD with SMKIs used in AML treatment that define the need for prophylaxis, what are the advantages and disadvantages of using non-triazole based prophylaxis, what is known about the safety ofempiric dose adjustments for SMKIs, and what the are the risks giving triazole with full-dose SMKI therapy.

How do targeted therapies alter the risk of invasive mold disease?

What are the risk with triazole antifungals?

Venetoclax

FLT3 inhibitors

What are the risks with echinocandins?

What are the risk with liposomal amphotericin B?

What is the promise of future antifungals?

What is the role of therapeutic drug monitoring?

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