How Can Hematologist-Oncologists Tackle Invasive Fungal Infections? Expert Insights from Clinical Practice

Interviewee:

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Support:	**The publication of this article was funded by Astellas.**
Disclosure:	Safah has received speaker honoraria from GSK, Sanofi, Incyte, Blueprint, and Pharmaessentia.
Acknowledgements:	Medical writing assistance was provided by Christos Evangelou, San Diego, California, USA.
Disclaimer:	The opinions expressed in this article belong solely to the interviewee. Important Safety Information can be found at the end of this article.
Keywords:	Antifungal therapy, hematologic malignancies, hematology/oncology, invasive fungal infections, isavuconazonium sulfate, risk factors.
Citation:	Microbiol Infect Dis AMJ. 2026;4[Suppl 1]:2-8. https://doi.org/10.33590/microbiolinfectdisam/VHVF1415

PHARMA PARTNERSHIP

Interview Summary

The diagnosis and management of invasive fungal infections in adult patients with hematological malignancies remains a challenge for hematology/oncology clinicians. In an interview with AMJ, Hana F. Safah of Tulane University School of Medicine, New Orleans, Louisiana, USA; Professor of Clinical Medicine at Louisiana State University, Baton Rouge; and the Director of the Stem Cell Transplantation Program and the Heme Malignancy at Our Lady of the Lake, Baton Rouge, Louisiana, USA, discussed the prevalence of invasive fungal infections in hematology/oncology patients, noting a 15% incidence rate in her practice. Risk factors include prolonged neutropenia, high-dose corticosteroids, environmental factors, and the use of emerging immunosuppressive therapies. The nonspecific presentation of fungal infections often hinders the timely diagnosis of invasive fungal infections. Safah highlighted the importance of a risk-adapted

approach to management and treatment. She also discussed a treatment option for the management of invasive fungal infections, including clinical considerations for its use. Key unmet needs in the diagnosis of invasive fungal infections in adult hematology/oncology patients include the scarcity of rapid diagnostic tools, a limited understanding of the epidemiology of infections, and research gaps regarding treatment outcomes in diverse patient populations.

INTRODUCTION

The complexities of managing invasive fungal infections in immunocompromised patients present several challenges for hematologist-oncologists, according to Safah. Safah shared her insights from her oncology practice in Louisiana, noting that the humid environment, combined with frequent natural disasters, increases the risk of invasive fungal infections in immunocompromised patients.

In a single-center, retrospective cohort study of adults and pediatric patients with relapsed or refractory acute lymphoblastic leukemia who received chemotherapy between 2014 and 2019, the incidence of invasive fungal infections was 12.1 infections per 10 patient-years.[1] However, Safah emphasized that the incidence can be much higher in some areas, including Baton Rouge, where she practices. "In my practice, invasive fungal infection is a common diagnosis," she said, adding that the humid environment may contribute to this high frequency.

Safah added that the incidence of fungal infections among patients with cancer has been on the rise in recent years,[2] and that the introduction of new therapies for hematological cancers has created new patient populations at risk for infectious complications. Her patients with invasive fungal infections include those receiving immunosuppressive therapies. "Patients treated with cell therapies are a new patient population that should be followed for infectious complications," she emphasized.

RISK STRATIFICATION

Risk factors for invasive fungal infections include prolonged neutropenia, prolonged treatment with corticosteroids, and transplant-related immunosuppression.[3] Safah advocates for a more comprehensive approach to risk assessment. Her risk stratification incorporates factors such as environmental exposure, socioeconomic status, and existing comorbidities. Environmental factors and occupational exposures play an important role in infection risk,[4] but many clinicians do not adequately incorporate these considerations into their patient risk assessments, Safah noted. When evaluating her patients, she considers workplace exposures, water damage from natural disasters, and housing conditions that may harbor mold, in addition to clinical risk factors. Iron overload from frequent transfusions and underlying lung disorders, such as COPD, also contributes to the risk of infections.[5,6]

When evaluating risk for invasive fungal infections in her patients with hematological malignancies, Safah considers age, disease characteristics, and treatment intensity to guide her treatment decisions.

DIAGNOSTIC CHALLENGES

Safah said the diagnosis of invasive fungal infections is challenging, as patients often present with nonspecific symptoms. She elaborated that the initial presentation of invasive fungal infections often mimics bacterial or viral infections, requiring

clinicians to systematically rule out these more common pathogens before considering fungal etiology. This diagnostic complexity, she went on, is compounded by the high mortality associated with delayed diagnosis and antifungal treatment,[7,8] all of which place pressure on hematologist-oncologists caring for immunocompromised patients.

The diagnostic approach for invasive fungal infections relies on histopathologic/cytologic and culture examination of tissue and fluid specimens, until molecular tools are more widely used in clinical laboratories.[9] Safah noted that while blood cultures are readily available, they have limited utility in diagnosing mold infections, and that invasive procedures, such as bronchoscopy and tissue biopsy, provide a definitive diagnosis but are not always feasible.[9] Safah advises her colleagues to obtain biopsy samples whenever possible, as they can confirm the diagnosis and reveal which species has caused the infection.[9] Molecular diagnostic methods, including PCR-based assays, can provide rapid diagnosis but are costly and not widely available.[10] However, Safah emphasized the value of molecular diagnostics in timely treatment initiation for antifungal infections.

According to Safah, timely diagnosis is a challenge in the management of invasive fungal infections. She explained that clinicians are limited in their ability to make a timely diagnosis and determine the species causing the infection. The development of rapid, accurate diagnostic tools could help improve outcomes in patients with invasive fungal infections by enabling timely diagnosis and treatment initiation. She added that epidemiological gaps limit our understanding of the impact of social determinants of health on infection risk and outcomes.

A TREATMENT OPTION IN CLINICAL PRACTICE

Safah noted that the introduction of isavuconazonium sulfate has provided clinicians with a useful addition to the antifungal treatment landscape. In her practice, she uses isavuconazonium sulfate to treat invasive aspergillosis and invasive mucormycosis in adults.[11] Contraindications include hypersensitivity to isavuconazole, coadministration with strong CYP3A4 inhibitors (such as ketoconazole or high-dose ritonavir) or strong CYP3A4 inducers (such as rifampin, carbamazepine, St. John's wort, or long-acting barbiturates), and use in patients with familial short QT syndrome.[11]

Isavuconazonium sulfate is the first FDA-approved azole antifungal for mucormycosis.[11] The single-arm, open-label VITAL trial demonstrated the efficacy of isavuconazonium sulfate in treating invasive mucormycosis.[12] Thirty-seven patients had proven or probable mucormycosis according to criteria based on those established by the European Organisation for Research and Treatment of Cancer/Mycoses Study Group.[11] The patients were White (68%), male (81%), and had a mean age of 49 years (range: 22–79 years).[11] Fifty-nine percent of patients had pulmonary disease involvement, half of whom also had other organ involvement. For patients with invasive mucormycosis, all-cause mortality through Day 42 was 38% (14/37).[11] Overall response success rate at end-of-treatment in this population was 31% (11/35).[11] These results provide evidence that isavuconazonium sulfate is effective for the treatment of mucormycosis. However, the efficacy of isavuconazonium sulfate for the treatment of invasive mucormycosis has not been evaluated in concurrent, controlled clinical trials.[11]

The Phase III SECURE trial was a randomized, double-blind, international, multicenter, non-inferiority study that compared isavuconazonium sulfate with voriconazole for the primary treatment of invasive mold disease.[13] The study demonstrated non-inferiority of isavuconazonium sulfate to voriconazole for the treatment of invasive aspergillosis.[13] Patients were stratified by history of allogeneic bone marrow transplant, uncontrolled malignancy at baseline, and

geographic region.[11] Baseline risk factors included hematologic malignancy (60%), T cell immunosuppressant use (49%), allogeneic hematopoietic stem cell transplant (35%), neutropenia (27%), corticosteroid use (27%), and diabetes (11%).[11] The mean age of patients was 51 years (range: 17–87 years), and the majority were Caucasians (78%), male (60%), with fungal disease involving the lungs (95%).[11] All-cause mortality through Day 42 in the overall intention-to-treat population was 18.6% (48/258) in the isavuconazonium sulfate treatment group and 20.2% (52/258) in the voriconazole treatment group for an adjusted treatment difference of −1.0% with a 95% CI of −8.0–5.9%.[11]

Warnings and precautions include hepatic adverse drug reactions requiring liver function monitoring at baseline and during treatment, infusion-related reactions that may require discontinuation of intravenous (IV) administration, hypersensitivity reactions, embryo–fetal toxicity requiring effective contraception in females of reproductive potential, and drug interactions that may alter concentrations of concomitant medications.[11] In addition, following dilution, the IV formulation may form insoluble particulates. Therefore, isavuconazonium sulfate should always be administered through an in-line filter to mitigate this risk.[11] See below for additional information regarding these safety considerations.

In a total of 403 adult patients treated with isavuconazonium sulfate in two clinical trials, the most frequent adverse reactions were nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated liver chemistry tests (16%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%).[11] Serious adverse reactions occurred in 55% (223/403) of patients, with 14% (56/403) discontinuing treatment because of adverse reactions.[11]

Dose adjustments are not required for mild or moderate hepatic impairment (Child-Pugh Class A and B), or for those with mild, moderate, or severe renal impairment, including end-stage renal disease.[11] Isavuconazonium sulfate has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and should be used in these patients only when the benefits outweigh the risks.[11] Safah added that when invasive aspergillosis or invasive mucormycosis is suspected in high-risk patients, isavuconazonium sulfate may be initiated while awaiting diagnostic confirmation. Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to initiating antifungal therapy to isolate and identify causative organisms.[11] However, therapy may be instituted before the results of cultures and other laboratory studies are known. Once these results become available, antifungal therapy should be adjusted accordingly.[11] "This approach allows for prompt treatment initiation in critically ill patients while ensuring appropriate targeted therapy based on confirmed diagnosis," Safah said.

DOSING CONSIDERATIONS

The FDA-approved loading dose is 372 mg, which is one reconstituted vial when administered as an intravenous formulation, every 8 hours for six doses, followed by maintenance treatment with one reconstituted vial (372 mg) daily.[11] Safah explained that the bioequivalence of IV and oral formulations allows transition between formulations without reloading.[11] Pharmacokinetic studies demonstrated predictable drug exposure with an absolute bioavailability of 98% after oral administration.[11]

DRUG INTERACTIONS AND SAFETY CONSIDERATIONS

Safah explained that the management of drug–drug interactions in hematology/oncology patients requiring antifungal therapy, who are typically on complex medication regimens, can be challenging.

Isavuconazole is a sensitive substrate of CYP3A4, and CYP3A4 inhibitors or inducers may alter the plasma concentrations of isavuconazole.[11,14] In addition, isavuconazole is a moderate inhibitor of CYP3A4 and a mild inhibitor of P-glycoprotein and organic cation transporter 2.[11] Drug interaction studies were conducted to investigate the effect of coadministered drugs on the pharmacokinetics of isavuconazole and the effect of isavuconazole on the pharmacokinetics of coadministered drugs. For example, isavuconazonium sulfate can increase the levels of immunosuppressive medications commonly used in transplant patients.[11] Safah advises use with caution, close monitoring, and potential dose adjustments in transplant patients undergoing immunosuppressive treatment who may require treatment with isavuconazonium sulfate.

Safah also emphasized the importance of collaborative care in the management of polypharmacy in hematology/oncology patients. "I have a PharmD in my practice who reviews my orders and looks for known drug–drug interactions," she said.

CONCLUSION

Safah concluded by emphasizing that the management of invasive fungal infections in adult hematology/oncology patients requires an understanding of the evolving epidemiology and therapeutic options, maintaining a high index of suspicion, and using a comprehensive diagnostic approach that combines imaging and biomarkers. She also highlighted the importance of individualized, risk-adapted care to address the real-world complexities of managing invasive fungal infections in hematology/oncology patients.

- CRESEMBA shortened the QTc interval in a concentration-related manner. CRESEMBA is contraindicated in patients with familial short QT syndrome

WARNINGS AND PRECAUTIONS

Hepatic Adverse Drug Reactions (e.g., elevations in ALT, AST, alkaline phosphatase, total bilirubin) have been reported in clinical trials and were generally reversible and did not require discontinuation of CRESEMBA. Cases of severe hepatic adverse drug reactions including hepatitis, cholestasis or hepatic failure including death have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with azole antifungal agents, including CRESEMBA. Evaluate liver tests at the start and during therapy. Monitor patients who develop liver abnormalities during CRESEMBA therapy for severe hepatic injury. Discontinue if clinical signs and symptoms consistent with liver disease develop that may be attributable to CRESEMBA.

Infusion-Related Reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during intravenous administration of CRESEMBA. Discontinue the infusion if these reactions occur.

Hypersensitivity Reactions: Anaphylactic reactions, with fatal outcome, have been reported during treatment with CRESEMBA. Serious skin reactions, such as Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue CRESEMBA if anaphylactic or serious skin reactions occur, and initiate supportive treatment as needed.

Embryo-Fetal Toxicity: During pregnancy, CRESEMBA may cause fetal harm when administered, and CRESEMBA should only be used if the potential benefit to the patient outweighs the risk to the fetus. Women who become pregnant while receiving CRESEMBA are encouraged to contact their physician.

Drug Interactions: Coadministration of CRESEMBA with strong CYP3A4 inhibitors such as ketoconazole or high-dose ritonavir and strong CYP3A4 inducers such as rifampin, carbamazepine, St. John's Wort, or long acting barbiturates is contraindicated.

Drug Particulates: Following dilution, CRESEMBA intravenous formulation may form precipitate from the insoluble isavuconazole. Administer CRESEMBA through an in-line filter.

ADVERSE REACTIONS

In adult patients, the most frequently reported adverse reactions among CRESEMBA-treated patients were nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated liver chemistry tests (16%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%).

In adult patients, the adverse reactions which most often led to permanent discontinuation of CRESEMBA therapy during the clinical trials were confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnea (0.5%), epilepsy (0.5%), respiratory failure (0.5%), and vomiting (0.5%).

In pediatric patients, the most frequently reported adverse reactions were diarrhea (26%), abdominal pain (23%), vomiting (21%), elevated liver chemistry tests (18%), rash (14%), nausea (13%), pruritus (13%), and headache (12%).

In general, adverse reactions in pediatric patients (including serious adverse reactions and adverse reactions leading to permanent discontinuation of CRESEMBA) were similar to those reported in adults.

Please see full Prescribing Information for CRESEMBA (isavuconazonium sulfate).

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