Preventing Invasive Fungal Infections in Hematologic Patients

BY SEEMA ARUN MEHTA, MD, MS

Invasive fungal infections (IFIs) are common, preventable infections in those oncology patients who receive hematopoietic stem cell transplantation (HSCT) or therapies for hematologic malignancies. The highest risk periods of neutropenia and graft-versus-host disease (GVHD) treatment, host immune function, prevention strategies, treatment modalities, donor types, and transplant complications can predispose patients to invasive infection with Candida and Aspergillus species (Curr Opin Oncol 2010;22(2):138-142). Both of these infections portend high morbidity and mortality, with attributable mortality at approximately 40 percent, even with new therapeutic drugs (BMC Infect Dis 2010;13:29; Emerg Infect Dis 2014;20(7):1149-1155; Med Mycol 2018;56(2):186-196; Crit Care 2015;19:7).

Tumor Mutation Burden & Checkpoint Inhibitors in MSI-H Colorectal Cancer

BY MARWAN FAKIH, MD

Mismatch repair protein deficiency (MMRD) or microsatellite instability-high (MSI-H) occurs in about 5 percent of metastatic colorectal cancers while higher frequencies are described in patients with earlier stages of disease (J Gastrointest Oncol 2018;9(4):610-617, Science 2017;357(6349):409-413). The drop in frequency in MSI-H cancers across increasing stages of colorectal cancer reflects the inherent good prognosis of earlier stage MSI-H, which is attributed to a robust tumor immune response.

MSI-H is characterized by increased tumor mutation, increased frameshift mutations, and insertion-deletion (indel) alterations. This leads to an increased incidence of neoantigen formation, which leads to a robust anti-tumor immune response. The recognition of an immune-overdrive status in MSI-H tumors, characterized by increased intratumor cytotoxic T-cell infiltration (CD8+) and countered by increased intratumor checkpoint expression (PD-L1, CTLA-4, etc.) (Cancer Discov 2015;5(1):43-51) led to the investigation of multiple checkpoint inhibitors in this group of patients.

SIRT1 Plays Key Role in Chronic Myeloid Leukemia

Patients with chronic myeloid leukemia (CML) can be treated with tyrosine kinase inhibitors. While these effective drugs lead to deep remission and prolonged survival, primitive leukemia stem cells resist elimination during the remission and persist as a major barrier to cure.

As a result, the majority of patients with CML require indefinite inhibitor treatment to prevent disease recurrence. They also face risks of noncompliance, toxicity, and financial burden. Development of effective therapeutic strategies to improve patient outcomes for CML and related cancers depends on identifying the key mechanisms that contribute to the persistence of these leukemic stem cells.

In a study published in the Journal of Clinical Investigation, Ajay Abraham, PhD, Shaowei Qiu, MD, Ravi Bhatia, MD, and colleagues at the University of Alabama at Birmingham (UAB) show how the stress-responsive protein SIRT1 plays important roles in maintaining the regenerative potential of CML leukemic stem cells and promoting leukemia development in CML (2019; https://doi.org/10.1172/JCI127080).

“Our studies provide a conceptual advance and new biological insights regarding the activity of SIRT1 and its role in CML leukemic stem cells,” said senior author Bhatia. At UAB, Bhatia is Professor of Medicine, Director of the Division of Hematology and Oncology, and Interim Director of the O’Neal Comprehensive Cancer Center.

In 2012, Bhatia and colleagues reported that SIRT1 was overexpressed in CML leukemic stem cells compared to normal hematopoietic stem cells, and this overexpression contributed to...
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Decades of translational and clinical study have led to the currently accepted paradigms for preventing fungal infections. Unfortunately, gaps still exist due to difficulties in administering drugs and implementing prevention paradigms, as well as increasing antifungal resistance. The focus here is on the gaps and challenges in current prevention strategies, including drug–drug interactions and toxicities, as well as a discussion on new drugs in development that may have a potential role in preventing IFIs in these vulnerable patients.

Current Prevention Challenges

Currently, there are a handful of drugs that are used to prevent and treat IFIs among oncology patients. The firstazole shown to prevent Candida infections in randomized trials (N Engl J Med 1992;326(13): 845-851; J Infect Dis 1995;171(6):1545-1552), fluconazole, continues to be frequently used for prevention. While the strengths of this drug include tolerability, flexibility in oral and IV formulations, predictable drug interactions, and generic costs, the largest gap is its spectrum of activity, which misses all molds.

While early randomized trials showed some activity foritraconazole in preventing molds as well as yeasts, this agent is poorly tolerated and in some settings has been associated with poor outcomes (Blood 2004;103(4):1527-1533; Clin Microbiol Infect 2011;17(Suppl 2):1-24; Ann Intern Med 1993;118(7):495-503). The newer azoles, posaconazole and voriconazole, have been shown to have activity in preventing both Candida and Aspergillus in randomized trials. However, when used in this setting, they have variable degrees of limitations associated with bioavailability, toxicities, and drug interactions.

Other antifungal agents that we use occasionally are echinocandins and liposomal amphotericin. Both have good activity profiles against yeasts. However, the currently available echinocandins suffer from inconsistent activity against molds, with increasing reports of breakthrough infection (Clin Microbiol Infect 2010;16(8):1191-1196; J Infect 2012;64(4):424-429). Lack of oral formulations and requirements for daily infusions have limited the enthusiasm and use of these drugs as long-term prophylactic agents.

New drugs, if shown to be effective and tolerable, could displace our currentazole and TMP/SMX paradigm for preventing a broad range of fungi that present dangerous health risks in hematologic and transplant patients.

Other toxicities, especially nephotoxicities, limit the use of long-term amphotericin formulations for prevention. Thus, the current guidelines committees have supportedazole drugs (fluconazole, posaconazole, and voriconazole) for prophylaxis against IFIs, with variable strengths given risks for mold infections and tolerability (Ann Hematol 2018;97(2):197-207; Clin Microbiol Infect 2011;17(Suppl 2):1-24).

Our approach to choosing prophylaxis is often iterative, with drugs chosen based on risks and ability to administer agents in a complex therapeutic setting. Theazole agents are preferred largely because of their ease of administration—all can be given orally. However, these drugs are often accompanied by toxicities, including hepatotoxicity, visual disturbances, neurotoxicity, prolongation of QT interval, as well as nausea, headaches, dyspepsia, and dysgeusia. Furthermore, when these drugs are combined with chemotherapeutic or immunosuppressive (IS) agents, toxicities can be amplified.

Somechemotherapeutic or IS drugs directly interact with the azoles, adversely impacting the metabolism of one or both drugs. Azole antifungals are not only a substrate for and inhibitors of cytochrome P450 (CYP450) enzymes, but they are also inhibitors of various membrane transporters (an example includes P-glycoprotein). Activation or inhibition of CYP450 enzymes has the potential to modify the pharmacokinetic profile of the drugs involved. This can result in either overdosing with subsequent toxicity or underdosing with subtherapeutic levels and consequent lack of efficacy (Clin Infect Dis 2009;48(10):1441-1458).

The anticipation of drug-drug interactions with azoles and chemotherapeutic or immunosuppressive agents can prevent toxicities while achieving maximal therapeutic effects when treating malignancy and in the immunocompromised patient. Therapy regimens using theazole or the chemotherapeutic/IS drug(s) (if such assays are available) is a means by which to identify the extent of interactions and help resolve real and/or potential problems by guiding dosing to optimize therapy and prevent subtherapeutic or supratherapeutic levels (Clin Infect Dis 2009;48(10):1441-1458).

The risk of pharmacokinetic interactions between azoles and other drug classes can vary depending on the drugs involved. Thus, not all azoles are created equal in their propensity to induce or inhibit CYP450 enzymes or inhibit membrane transporters. Many of the interactions encountered between azoles and chemotherapeutic or IS agents often render it impossible to use the azoles, requiring alternatives, such as echinocandins.

The echinocandins, however, are administered intravenously daily, thus possibly posing a barrier to outpatient administration. Although echinocandins seem to have a much safer toxicity profile than azoles, and less drug–drug interactions with currently available chemotherapeutic and antifungal drugs, microbial resistance is growing. This is thought to be due in part to low doses given, poor penetration into various tissue compartments, and ultimately therapeutic failure (Clin Microbiol Rev 2014;27(1):68-88).

New alternative drugs are necessary to prevent both Candida and Aspergillus. Attractive features would include a more convenient dosing schedule with a broad spectrum of activity against both molds and yeasts, and a high barrier to resistance. An barrier to resistance would also have minimized toxicities and lack interaction with chemotherapeutic or IS agents, especially those with complex interactions with CYP450 enzymes.

Pneumocystis Species

Pneumocystis pneumonia (PCP) is a fungal infection that is routinely treated prophylactically in those undergoing HSCT and, in some instances, amongst those receiving chemotherapeutic or various IS drugs. Drugs such as trimethoprim/sulfamethoxazole (TMP/SMX), dapsone, atovaquone, or pentamidine (inhaled or IV) are frequently used as prophylaxis. These agents, however, are accompanied by multiple toxicities that often make them difficult to take, including fever, rash (often resembling cutaneous GVHD), neutropenia, pancytopenia, nephrotoxicity, hepatitis, hyperkalemia, methemoglobinemia, rash, bronchospasm (with the use of inhaled pentamidine), hemolytic anemia in those who are glucose-6-phosphate dehydrogenase (G6PD) deficient, and anaphylaxis. Though dapsone, atovaquone, and pentamidine are often used in those intolerant of TMP/SMX (the prophylactic agent of choice), we have seen breakthrough pulmonary and extra-pulmonary PCP develop while patients are on these drugs (J Antimicrob Chemother 2016;71(9):2397-2404).

Interestingly, PCP is an infection with a “non-classic,” inferred susceptibility to echinocandins. The echinocandins exhibit in vitro activity against the cyst forms of PCP. This is attributed to these drugs’ ability to inhibit the synthesis of beta-1,3-D-glucan, which is in abundance in the cyst form of PCP but not the trophic forms (PLoS One 2010;5(1):e8524).

Emerging Antifungal Approaches

Rezafungin is a novel antifungal echinocandin being investigated in phase III studies to evaluate its role as a treatment for candidemia and invasive candidiasis, as well as its utility as a prophylactic agent against IFIs (J Glob Antimicrob Resist 2018;14:58-64). While current echinocandins are known to be excellent candidal drugs, they have significant limitations, as previously mentioned.

Rezafungin is a once-weekly, IV antifungal with a unique pharmacokinetics profile due to its long half-life (approximately 130 hours), allowing for a more convenient dosing schedule and for use on an outpatient basis. Furthermore, phase I studies have demonstrated that the
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drug can be given at higher doses than most echinocandins without the toxicities associated with other echinocandins at lower doses (J Glob Antimicrob Resist 2018;14:58-64).

Rezafungin is an analogue of anidulafungin, but with structural differences that lead to increased chemical stability and lack of reactive intermediates that may potentially contribute to toxicity (J Glob Antimicrob Resist 2018;14:58-64). It has a broad spectrum of activity with demonstrated potent in vivo activity against Candida species, Aspergillus species, Pneumocystis, and other less commonly encountered but clinically relevant molds. It is unique in that it has activity against Aspergillus species, and other less commonly encountered dangerous health risks in hematologic disease, and its prevalence is rising among stem cell and solid organ transplant recipients.

Conclusion
IFIs carry significant morbidity and mortality amongst HSCT recipients and those with hematologic malignancies. Our current prevention strategies are good, but not excellent. There are gaps that remain, making these patient populations vulnerable to IFIs. Furthermore, with the development of newer chemotherapeutic agents, we are observing numerous drug-drug interactions with the standard-of-care azoles. Additionally, the antifungal agents utilized most often are not benign drugs and are often associated with side effects and toxicities that need to be balanced by the prophylactic benefits that the drugs offer.

While we are familiar with a host of prophylactic drugs, there are newer, novel drugs on the horizon that offer potential advantages to our patients. These drugs, if shown to be effective and tolerable, could displace our current azole and TMP/SMX paradigm for preventing aminocandidin infections. rezafungin could serve as a once-weekly replacement of azoles and TMP/SMX as prophylaxis, generating improvements in drug compliance, drug interactions, and toxicities. Overall, the drug has the potential to be a promising new approach for IFI prophylaxis amongst those with HSCT and hematologic malignancies.

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NEED FOR MORE EFFECTIVE THERAPIES
There is an increasingly urgent need to develop new therapies for IFIs, particularly medications that can be used to prevent fungal infections among patients with compromised immune systems.

ON THE RISE
An increasing number of people in the U.S. have compromised immune systems, putting them at greater risk for IFIs: 
• Hospitalized patients
• Patients undergoing surgery
• Cancer or transplant patients
• Patients with chronic diseases
Rates of invasive candidiasis are difficult to estimate and can vary based on race, region, and study type.

ON THE RISE
Candidate auro (C. auris) is an emerging drug-resistant fungus that spreads, infects, and can cause serious and deadly infections in over a dozen countries.

BY THE NUMBERS
• Invasive candidiasis (Candida) is a common hospital-acquired infection in the U.S., resulting in about 40,000 cases each year.
• Invasive aspergillosis (Aspergillus) most often in people with weakened immune systems or lung disease, and its prevalence is rising among stem cell and solid organ transplant recipients.

THE IMPACT OF INVASIVE FUNGAL INFECTIONS
We often think of fungal infections as simply bothersome conditions such as athlete’s foot or toenail fungus. But certain types of fungal infections, known as “invasive fungal infections” (IFIs), can be dangerous and fatal. IFIs are systemic and are typically caused when fungi invade the body in various ways such as through the bloodstream or by the inhalation of spores. IFIs can also spread to many other organs such as the lung and kidney. They are associated with serious illness and death, rising drug resistance and increasing healthcare costs.

A GROWING GLOBAL HEALTH THREAT
Annual Worldwide Deaths from IFIs >1.5 MILLION
The Centers for Disease Control and Prevention estimate the number of deaths from drug-resistant bacterial and fungal infections cost the US approximately $20 to $25 billion annually.

15 to 65% mortality
Nearly 90% of IFI-related deaths

NOW AVAILABLE ON THE CME PATHWAYS
For more information about serious fungal diseases, please visit the CDC website at: cdc.gov/fungal.