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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* 2013;13;29; *Emerg Infect Dis* 2014;20(7):1149-1155; *Med Mycol* 2018;56(2):186-196; *Crit Care* 2015;19:7).

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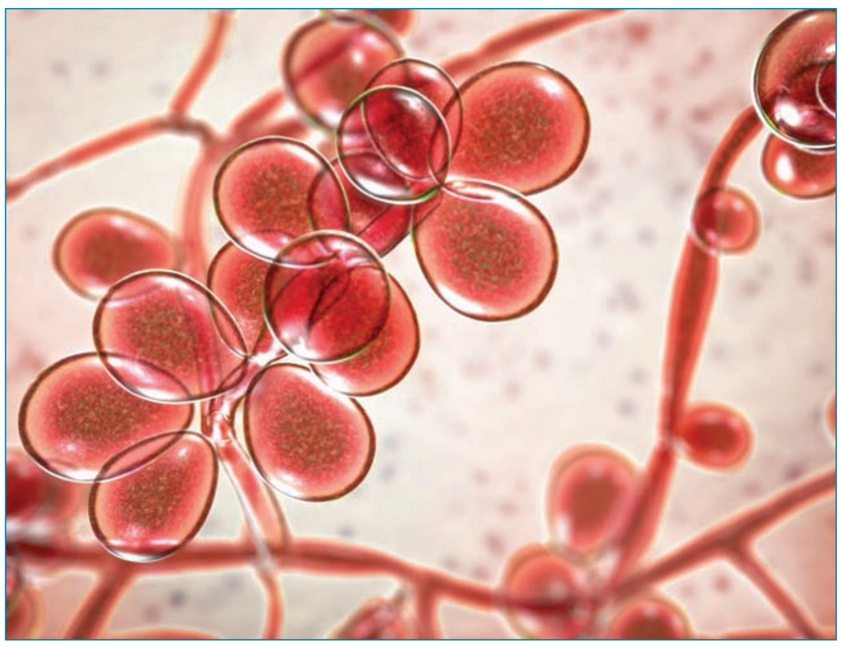

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Tumor Mutation Burden & Checkpoint Inhibitors in MSI-H Colorectal Cancer

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.

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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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Preventing Invasive Fungal Infections in Hematologic Patients

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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 first azole 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 for itraconazole 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.

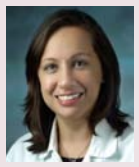
Other antifungal agents that we use occasionally are echinocandins and liposomal amphotericin. Both have good activity profiles against yeasts. However, the currently available echinocandins suffer from inconsistent activity against molds, with increasing reports of breakthrough infection (*Clin Microbiol 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 current azole and TMP/SMX paradigm for preventing a broad range of fungi that present dangerous health risks in hematologic and transplant patients.

Other toxicities, especially nephrotoxicities, limit the use of long-term amphotericin formulations for prevention. Thus, the current guidelines committees have supported azole 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. The azole 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.

Some chemotherapeutic 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).



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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 IFIs concurrently. Therapeutic drug monitoring of either the azole 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 IS 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 ideal agent 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 chemotherapy or various IS drugs. Drugs such as trimethroprim/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).

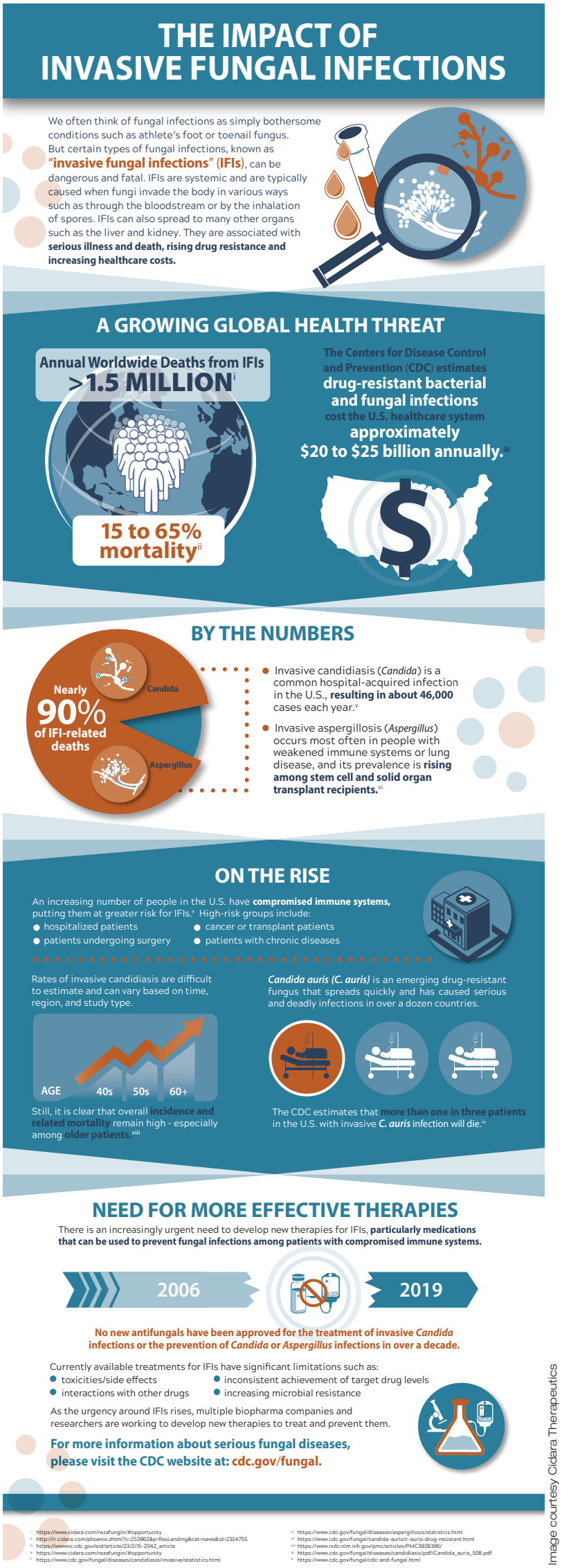
Rezafungin is an analogue of anidulafungin, but with structural differences that lead to increased chemical stability and lack of reactive intermediates that may potentially contribute to toxicity (*J Glob Antimicrob Resist* 2018;14;58-64). It has a broad spectrum of activity with demonstrated potent *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 PCP—cyst and trophic forms—making it an effective prophylactic agent against this microbe (*Blood* 2016;128:339).

Because of its spectrum of activity and its unique pharmacokinetics, 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.

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 a broad range of fungi that present dangerous health risks in hematologic and transplant patients. OT



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