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REVIEW ARTICLE

The current landscape of invasive mold infections in neutropenic patients with hematologic malignancies

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ABSTRACT

Invasive mold infections are a significant cause of morbidity and mortality among patients with hematologic malignancies, primarily due to the prolonged periods of profound neutropenia that characterize these diseases. As our population continues to age, the incidence of hematologic malignancies is expected to rise, further exacerbating the public health burden posed by fungal infections. Therefore, it is crucial to enhance our understanding of the landscape of invasive mold infections and the underlying mechanisms by which this patient population becomes infected. Such knowledge is essential for developing effective prevention strategies and improving the management of these infections in hematologic malignancies. This review will examine the reasons why patients with hematologic malignancies represent an at-risk population for invasive mold infections, with a particular focus on the deficiencies in the host immune system. We will also address some of the challenges associated with diagnosing these infections in a vulnerable population and review current and emerging technologies aimed at improving detection. Lastly, this review will evaluate the current literature on prophylaxis and treatment options, as well as more novel therapies under development.

Introduction

Hematologic malignancies are the fourth most common cancer type and make up about 10% of all diagnosed cancers in the United States each year[1,2]. Globally, the incidence of hematologic malignancies has been increasing since 1990 and is projected to increase in the future[3,4]. Life expectancy is projected to reach 80 years by 2040, and as our population continues to live longer, more of the elderly are at risk for hematologic malignancy, in particular acute myeloid leukemia, non-Hodgkin lymphoma, and myelodysplastic syndrome, that have a mean age of diagnosis ranging from 67-70 years[2]. Although survival outcomes have improved with the development of more effective treatment strategies, current treatment involving intensive chemotherapy and hematopoietic stem cell transplantation renders patients severely neutropenic for prolonged periods of time, placing patients at increased risk for invasive fungal infections (IFI). Through improvement in our supportive care and treatment strategies, expert practitioners are more comfortable taking older patients to transplantation, with the number of patients >60 years old undergoing hematologic stem cell transplant (HSCT) having doubled in the period of 2007 to 2013 compared to an earlier period of 2000 to 2006[5]. With attendant neutropenia and immune suppression associated with HSCT, utilization of the technology has further increased the at-risk population for invasive fungal infections. Fungal infections are among the most serious complications in neutropenic patients resulting in significant morbidity and mortality. This review will explore the landscape of invasive mold infections in neutropenic patients with hematologic malignancies. We will discuss the epidemiology, risk factors, and clinical manifestations of invasive mold infections in this population, as well as examine effective preventive strategies, diagnostic modalities, and current and future perspectives in treatment approaches. It is crucial to have this understanding of mold infections in neutropenic patients with hematologic malignancies, because as the incidence of hematologic malignancies rises and the success of treatment protocols continues to improve, addressing the threat of invasive molds is necessary in order to enhance patient outcomes and quality of life.

Background

Leukocytes are integral components of both the innate and humoral immune system. These cells, categorized into myeloid and lymphoid lineages, include granulocytes such as neutrophils, eosinophils, and basophils; as well as B- and T-cells, respectively[6]. Neutrophils play a pivotal role in the innate immune response and serve as one of the primary lines of defense against fungal and bacterial infections. The mechanisms of action include phagocytosis, the production of reactive oxygen and nitrogen species, the formation of neutrophil extracellular traps, and the secretion of pro-inflammatory cytokines[7]. Neutropenia is characterized by an absolute neutrophil count (ANC) of less than 1.0 $x10^9$/L, with severe neutropenia defined as an ANC below 0.5$x10^9$/L, and profound neutropenia as an ANC below 0.1$x10^9$/L[8]. Patients with cancer often experience neutropenia, significantly increasing their susceptibility to infections, resulting in a high risk of mortality. Febrile neutropenia is an oncologic emergency, and in many cases, fever may represent the only sign of infection, with only 30-50% of cases identifying an infectious source[9]. While both solid and hematologic malignancies can lead to the development of febrile neutropenia, it is more frequently observed in patients with hematologic malignancies.

Patients with hematologic malignancies, including leukemias, multiple myeloma, lymphomas, and myelodysplastic syndrome (MDS), are at increased risk of neutropenia from both the disease and its treatment. Frequently, normal bone marrow function is replaced by a clonal proliferation of neoplastic cells, resulting in bone marrow infiltration with associated neutropenia and, at times, impaired granulocyte function as well[10]. The treatment

regimens for these cancers include intensive doses and combinations of chemotherapeutic agents that induce prolonged neutropenia. Consequently, patients with hematologic malignancies experience more frequent, prolonged, and severe neutropenia, and it is well understood in the literature that the risk of developing more serious and complicated infections is linked to the depth and duration of neutropenia[11]. Studies estimate that 10%-50% of patients with solid tumors and up to 80% with hematological malignancies receiving chemotherapy develop febrile neutropenia[12]. In a retrospective analysis derived from a national database, the authors Makhani et al noted that hematologic malignancies had the highest incidence of admissions for febrile neutropenia compared to solid tumors[13]. There are risk stratification tools such as the Multinational Association for Supportive Care in Caner (MASCC) risk index, and Infectious Diseases Society of America (IDSA), National Comprehensive Cancer Network (NCCN), and American Society of Clinical Oncology (ASCO) guidelines that assess whether a patient is at high or low risk of serious medical complications related to febrile neutropenia. Per the IDSA guidelines, high-risk febrile neutropenia includes ANC less than 01.x x10^9/L expected to last more than seven days. This profound prolonged neutropenia is most likely seen in the pre-engraftment phase of patients receiving a hematologic stem cell transplant and in patients undergoing induction chemotherapy for acute myeloid leukemia[14].

Pathophysiology

As previously discussed, patients with hematologic malignancies are at significant risk for prolonged and profound neutropenia, which increases their susceptibility to life-threatening bacterial and IFI. Despite the widespread use of anti-fungal prophylaxis, IFI remain a major cause of morbidity and mortality among this patient population[15]. Notably, individuals with hematologic malignancies constitute a significant proportion of cases of invasive fungal infections worldwide, underscoring the urgent need to enhance our understanding of IFI within this demographic[16]. In a study by Rayens et al, transplant recipients and cancer patients represented two of the largest and most heavily affected cohorts at heightened risk of fungal diseases[17]. Fungi can occur as yeasts, molds, or as a combination of both forms. This review will focus specifically on invasive mold infections, which have emerged as the most prevalent causative pathogens of IFI in patients with various hematologic malignancies.

Mold is a microscopic fungus characterized by long filamentous structures called hyphae. Common types of molds include *Aspergillus*, *Fusarium*, *Mucor*, *Penicillium*, *Rhizopus*, among others. Mold is a natural part of the environment, thriving in areas of moisture and oxygen, such as soil, plants, decaying matter, and various indoor settings. Mold infections can manifest as a wide spectrum of diseases, ranging from superficial infections to invasive disseminated infections affecting critical organs such as the brain, heart, lungs, kidneys, and liver. Many invasive molds are challenging to diagnose early and often prove difficult to treat effectively. The severity of disease is influenced by several factors including the size of the inoculum, magnitude of tissue destruction, ability of the fungi to multiply in tissues, and immunologic status of the host[18,19]. Common portals of entry include the respiratory tract, gastrointestinal tract, and blood vessels. Fungi can infiltrate a host through traumatic entry or inhalation of spores, underscoring the need for vigilance in susceptible populations.

The body has a plethora of defenses to prevent fungal infiltration, with intact skin serving as both a physical barrier and a matrix for complex and intricate immunological network. Epithelial cells are proficient in recognizing fungi, and upon detection, they can initiate an immunological cascade[19]. In the respiratory and gastrointestinal tracts, mucous membranes are bathed in fluids with antimicrobial substances as well as lined with ciliated cells that actively remove foreign materials[18]. The host immune system is also equipped with pattern recognition receptors (PRR)

that detect pathogen-associated molecular pattern (PAMP) components of fungal cell walls. The interaction between host PRR and PAMPs triggers an immune response aimed at fighting fungal pathogens. Key cell types involved in antifungal defense include neutrophils, macrophages, dendritic cells, natural killer cells, innate-like lymphocytes, and epithelial cells. These cells are the first line of defense in the innate immune response. Fungal cells can be eradicated by macrophages that engulf pathogens and destroy them within phagolysosomes. Additionally, monocytes secrete chemokines and cytokines, and function as antigen-presenting cells (APC) to T-lymphocytes, thereby facilitating the adaptive immune response[20]. While there exists a comprehensive network of immunologic defenses against IFI, neutrophils are among the most critical components of the host defense system.

Neutrophils are among the most abundant leukocytes in blood and are rapidly recruited to sites of infection. They are effective in elimination of pathogens through phagocytosis, intracellular killing of microorganisms via oxidative and non-oxidative cytotoxic mechanisms, extracellular degranulation of pre-stored antimicrobials, formation of neutrophil extracellular traps (NETs), and production of pro-inflammatory and anti-inflammatory cytokines and chemokines[21]. Neutrophils are essential in combating IFI. As previously discussed, patients with hematologic malignancies often experience profound and prolonged neutropenia, significantly increasing the risk of invasive mold infections. In cases of the invasive mold *Aspergillus*, neutrophils are vital for the destruction of fungal hyphae. In a landmark paper by Diamond et al, the authors demonstrated how neutrophils attach to hyphae, spread across their surface, and degranulate[22]. Neutrophils also aggregate to inhibit spore germination[23]. In infections caused by the mold *Mucorales*, neutrophils cause spore and hyphal damage by releasing reactive oxygen metabolites, cationic peptides, and perforin. They also activate other immune cells to assist in *Mucorales* killing. *In vivo* studies in mice show that swollen *Rhizopus* spores induce neutrophil recruitment and inflammation. *In vitro* chemotactic studies show that swollen *Rhizopus* spores produce neutrophil chemotactic factors. While neutrophils also cause hyphal damage in *Rhizopus*, their efficacy is less than that observed against *Aspergillus* hyphae[24]. *Fusarium* is another lethal mold infection, and neutrophils are critical in combating these infections as well. As humans have evolved mechanisms to combat fungal infections, fungi have concurrently developed strategies to overcome and evade the innate immune system of humans. Some fungal cells can alter their surface layers to shield the highly conserved PAMPs, preventing recognition by PRRs[25]. Certain fungi can parasitize macrophages to escape phagocytosis, while others can form morphologically distinct structures to evade immune detection[20]. In the case of *Aspergillus fumigatus*, this mold initiates host infections using asexual spores known as conidia. Pinzan et al investigated the mechanism by which *Aspergillus* evades the immune response, revealing that surface proteins on conidia play a crucial role in immune evasion and modulation[26]. Additionally, resting spores of *Mucorales* exhibit minimal chemotactic properties to evade neutrophils detection.

Due to therapy-induced immunosuppression, patients with hematologic malignancies often receive extensive antibiotic treatment. Prophylactic antibiotics are typically initiated at the onset of intensive chemotherapy or shortly thereafter, once patients become neutropenic, to prevent bacterial infections. However, prolonged antibiotic exposure is thought to increase susceptibility to fungal infections. A Danish study identified prior antibiotic exposure as a risk factor of candidemia, a pseudohyphal organism[27]. In a study by Gong et al, patients who succumbed to mold infections had received more broad spectrum antibiotics compared to those who did not survive[28]. Although theirs was a prospective study done in an infant population, the association between prolonged antibiotic exposure and the increased risk of IFI[29] was demonstrated. Several studies have attempted

to elucidate the mechanism by which antibiotic exposure increases risk of IFI. Drummond et al used a mouse model to demonstrate that broad-spectrum antibiotics lead to gastrointestinal (GI) tract specific susceptibility to IFI. They discovered that pre-exposure broad-spectrum antibiotics impaired lymphocyte-dependent IL-17A- and GM-CSF-mediated antifungal immunity within the GI tract that was associated with increased mortality following a fungal challenge. Additionally, bactericidal antibiotics were shown to directly disrupt metabolic processes in myeloid cells, thereby limiting their ability to combat pathogens, including fungi. Furthermore, certain antibiotics may adversely affect and modulate the immune system. For instance, previous studies have associated vancomycin with defective immune response in both mice and in humans[30].

Epidemiology

The epidemiology of fungal infections varies significantly across the world and even within the United States[31,15]. Recent studies utilizing healthcare network data in the United States showed a mean incidence of IFI of 27.2 cases per 100,000 patients annually, with a mean annual increase of 0.24 cases per 100,000 patients. They demonstrated that *Aspergillus* was the most common IFI among patients with hematologic malignancies and HSCT recipients (35.2-49.5%)[32]. A different American study also showed that among patients with hematologic malignancies, the majority (31.9%) of IFI were aspergillosis and mucormycosis constituting 19.4% of cases[33]. A recent retrospective study conducted in Brazil revealed that among patients with hematologic malignancies and those undergoing stem cell transplantation, patients with acute leukemia had the highest frequency of IFI at 17.3%, and the most frequent IFI was the mold *Aspergillus* at 53.2%, followed by the mold *Fusarium* at 18.1%[34]. In Italy, a study involving 538 patients with hematologic malignancies with IFI found that approximately two-thirds of these infections were caused by a mold, and the majority of the mold infections were caused by *Aspergillus* (90%). *Zygomycetes* and *Fusarium* species accounted for 4% of cases, while the remaining mold infections were from *Scedosporium*, *Acremonium*, *Penicillium*, and *Cladosporium* species[16]. In a study at a single center in Iran evaluating patients with hematologic malignancies and mold infections, *Aspergillus* was the most common pathogen (85%) followed by *Mucorales* and *Fusarium*[35]. Similarly, a retrospective study in South Korea that included patients with AML and ALL, found that *Aspergillus* was the most frequently identified IFI, consistent with trends observed in other countries[36].

Even in the absence of a hematologic malignancy, there is a high rate of mortality from IFI among patients 65 years and older. Elderly patients are likely to be frail, have a greater number of chronic diseases, are more likely to be malnourished, and to have weakened barriers to pathogens, all of which increase their risk of infection. Furthermore, elderly individuals often experience polypharmacy, leading to more drug-drug interactions that may diminish the efficacy of anti-fungal prophylaxis[28]. A substantial proportion of patients with hematologic malignancies are elderly; for instance, the median age of patients with MDS is 70 and for AML is 69[1]. Consequently, older patients with hematologic malignancies are at even greater risk of IFI. A study in China explored IFI in elderly patients with or without malignancy, and not unexpectedly, the proportion of disseminated fungal infections increased significantly in the oldest age patient cohort of >80 years compared to 60-69 years and 70-79 years, and the highest all-cause mortality was identified in patients over 80 years old. In a multivariate regression analysis, they found that polypharmacy, CKD, broad-spectrum antibiotics, and lymphopenia were associated with mortality in the elderly patients with IFI[28].

Clinical manifestations and diagnosis

Clinical manifestations of invasive mold infections in neutropenic patients with hematologic malignancies can be varied and nonspecific, making it difficult to differentiate mold infections

from one another and from non-mold infections. The most common manifestation is fever, and depending on other sites of infection, can also include pulmonary symptoms (cough, pleuritic chest pain, hemoptysis, shortness of breath, etc.), sinusitis, skin or oral lesions, and ophthalmologic symptoms[37]. Consequently, consensus guidelines have removed particular localizing symptoms as criteria diagnostic of invasive mold infections. For instance, the most recent iteration of consensus guidelines from the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group Education and Research Consortium (MSGERC) only lists pain and the presence of a suspicious lesion as clinical criteria for diagnosis of sinonasal mold infection. On the other hand, it does not include any symptoms for the diagnosis of pulmonary or central nervous system mold infections[38,32].

Diagnosis of invasive mold infections in this population is multi-faceted and relies on a combination of clinical, serologic, microbiologic, and imaging-based findings. Due to clinical uncertainty, diagnosis of invasive mold infections relies on models that combine diagnostic data to provide a probability of invasive mold infections. In general, culture and histopathologic-based examination of a sterile site currently remains the gold standard for establishing the diagnosis of a proven invasive fungal infection; the most recent EORTC/MSGERC consensus definitions also include the identification of fungal elements on biopsy with concurrent amplification of fungal DNA by PCR and sequencing of mold-specific DNA as an additional means of establishing this diagnosis[38].

Blood cultures are obtained for virtually all neutropenic patients with hematologic malignancies who develop fever, but their yield is generally poor and varies across different mold infections. For example, although invasive aspergillosis is more common than invasive fusariosis, blood cultures are more frequently positive in patients with the latter[39,40]. This disparity has led to development more sensitive assays to improve diagnostic accuracy. For *Aspergillus*, the galactomannan antigen and *Aspergillus* polymerase chain reaction (PCR) assays are widely utilized and are part of mycological diagnostic criteria for probable invasive mold disease in the 2020 EORTC/MSGERC consensus definitions. The *Aspergillus* galactomannan assay can be performed in serum, blood, cerebrospinal fluid (CSF), and on bronchioalveolar lavage (BAL) specimens, and interpretation is based upon cutoff values and combination with other data. However, its sensitivity is reduced in non-neutropenic patients and those receiving mold-active prophylaxis[38,41,42]. The *Aspergillus* PCR assay can likewise be conducted on blood, plasma, CSF, and BAL specimens, with the additional advantage of being able to identify the specific species of *Aspergillus* and potentially detect mutations that confer antimicrobial resistance (Table 1)[38]. Similar assays to detect other invasive molds are commercially available in some contexts and are otherwise created by institution-specific laboratories to aid in diagnosis of these infections.

More broadly, evaluation of serum beta-D-glucan (BDG) has also proven to be effective in supporting the diagnosis of invasive mold disease, particularly in high-risk patients, and is included in the EORTC/MSGERC consensus definitions. White et al. conducted the largest meta-analysis evaluating BDG-based assays for the diagnosis of invasive fungal infections (not only including molds) and noted a pooled sensitivity of 80% and a pooled specificity of 63% among low-bias studies. Among the 19 studies included, there was considerable variability in positive predictive value, likely owing to the diverse patient populations in the included studies, but the negative predictive value for ruling out invasive fungal disease was consistently higher, generally greater than 90%[43]. Recent interest has likewise developed in microbial cell-free DNA-based assays, also commonly referred to as Karius testing, to aid in the diagnosis, typically performed on plasma samples (Table 1). Several retrospective analyses have assessed these assays and found them to be of reasonable diagnostic utility, particularly

for non-*Aspergillus* invasive mold infections[44,45]. However, to date, no prospective or randomized studies have been published. These assays exhibit more limited utility for detecting *Aspergillus* invasive mold infections. Although the assays are non-invasive, currently they are generally not able to sufficiently rule out invasive mold infections.

Table 1. Comparison of utility of various diagnostic approaches for evaluation of invasive mold infections.

	Sensitivity	Specificity	Guidelines
Blood culture[39,40]	5%	-	Included in consensus guidelines if a positive blood culture is in the setting of the appropriate clinical context (e.g. a clinical syndrome consistent with an invasive mold infection)
CT scan[38,46,47]	80-90%*	80-90%*	Several imaging findings included in consensus guidelines
Beta-D glucan[43]	50-95%	60-96%	Included in consensus guidelines with a single threshold
Galactomannan[38,41,42,**]	48-92%	85-95%	Included in consensus guidelines; interpretation depends on type of specimen and optical density thresholds
Karius[44,45]	44-90%	90-97%	Not included in consensus guidelines at this time

*Sensitivity and specificity depends on site of infection and what anatomic area is imaged.
**Only recommended presently for use in diagnosis of invasive aspergillosis.

Finally, imaging plays a crucial role in the diagnosis among patients with hematologic malignancies. Several imaging findings, including the "halo sign" to support the diagnosis of invasive pulmonary aspergillosis in neutropenic patients, are included in EORTC/MSGERC consensus definitions. High-resolution CT scans, in particular, have been emphasized for their superior diagnostic utility compared to conventional CT scans for evaluating invasive mold infections (Table 1)[38]. Other imaging findings, although not included in these consensus definitions, may also offer valuable diagnostic insights. For example, the "hypodense sign" evaluated by Sassi et al., demonstrated high sensitivity and specificity for diagnosing invasive pulmonary mold infections in neutropenic patients with hematologic malignancies, even in cases where other more commonly cited CT findings were equivocal[46]. Due to less widespread use, the utility of positron emission tomography-computed tomography (PET-CT) in this setting remains open for investigation. In a recent phase 3 randomized trial that compared fluorodeoxyglucose (FDG)-PET with conventional CT in patients receiving conditioning chemotherapy for hematopoietic stem cell transplant with persistent or recurrent fevers, patients in the FDG-PET group had more frequent meaningful changes in antimicrobial therapy; most notably, narrowing of antimicrobial therapy occurred in 43% of patients who underwent FDG-PET compared to 25% of patients in the CT group[47].

Prophylactic regimens

Several consensus statements (Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology, ASCO, IDSA) provide guidance on the use of mold-active prophylaxis, generally recommending it for patients with severe neutropenia (ANC below $0.5x10^9$/L) lasting more than 7 days. Commonly used agents include posaconazole, voriconazole, and isavuconazole (Table 2)[48,49]. This recommendation is based on several randomized trials, and ultimately a meta-analysis, that showed a reduction in incidence of invasive fungal infections and mortality related to such infections compared to fluconazole. However, this meta-analysis also showed an increase in adverse effects and did not show a reduction in overall mortality[50]. Among available agents, posaconazole has the most robust data supporting its use. In a large-

scale network meta-analysis, all mold-active azoles assessed were superior to fluconazole, and posaconazole was superior to voriconazole[51]. The efficacy of isavuconazole compared to posaconazole or voriconazole remains a subject of debate, with most large studies being retrospective[52].

Table 2. Comparison of utility of various mold-active agents for the treatment and prevention of invasive mold infections.

	Prophylaxis	Treatment	Considerations	Adverse effects
Voriconazole[48,49]	Yes	Yes (first-line for invasive aspergillosis)	Drug-level monitoring required; several drug-drug interactions	Dermatitis, hepatotoxicity, neurotoxicity, cutaneous malignancies, nephrotoxicity, QTc prolongation, periosteal disease
Isavuconazole[48,49]	Yes	Yes (first-line for invasive aspergillosis)	Drug-level monitoring required; several drug-drug interactions	QTc prolongation, peripheral edema, dermatologic toxicity, hypokalemia, gastrointestinal disturbance, hepatotoxicity
Posaconazole[48,49]	Yes	Yes	Drug-level monitoring required; several drug-drug interactions	QTc prolongation, hypertension, peripheral edema, fever, nephrotoxicity, herpes simplex virus infection, metabolic and gastrointestinal disturbance
Amphotericin[32,59]	No	Yes (first-line for mucormycosis)	Requires close monitoring of kidney function and electrolytes	Nephrotoxicity, hepatotoxicity, electrolyte derangements, hypersensitivity reactions (including anaphylaxis)
Micafungin[56]	Yes*	Yes	Does not require drug-level monitoring	Phlebitis, gastrointestinal disturbance, hematologic toxicity, nephrotoxicity, fever
Caspofungin[56]	No	Yes	Does not require drug-level monitoring	Cardiovascular toxicity, hematologic toxicity, gastrointestinal disturbance, hepatotoxicity, infusion reaction
Fosmanogepix[62]	No	Yes*	Currently under investigation	Nausea, hepatoxicity, neurotoxicity
Olorfim[62]	No	Yes*	Currently under investigation	Headache, dermatologic toxicity, hepatotoxicity, gastrointestinal disturbance

*Based on limited data/currently under evaluation and not currently recommended by consensus guidelines.

Despite reports of efficacy, concerns remain about the utility of mold-active prophylaxis, particularly due to drug-drug interactions between cancer-directed therapies and mold-active azoles that arise from cytochrome P450-mediated metabolism. Additional concerns include development of resistance to antifungal therapies, cost, and toxicity of these agents. Therapeutic drug level monitoring for various azoles is generally recommended to ensure therapeutic efficacy, minimize toxicity, and facilitate dose adjustments in the presence of drug-drug interactions. Among the most common drug-drug interactions in patients with hematologic malignancies involves venetoclax and azoles, requiring dose-reduction in order to maintain appropriate serum levels[53]. Although this has not been studied prospectively, retrospective studies have shown that failure to dose-reduce venetoclax

results in prolonged duration of cytopenias and associated complications[54]. Other commonly used medications in AML include FLT3 targeting agents midostaurin and gilteritinib. Metabolism of midostaurin and gliteritinib are also affected by CYP3A4 inhibition, although robust data to guide potential dose adjustment when administered concurrently with azoles are currently lacking. Nevertheless, dose reductions are advised for the AML drugs quizartinib and ivosidenib in this context[48]. The rate of breakthrough infections in patients receiving mold-active prophylaxis is varied; for instance, in a 4-year study of patients receiving posaconazole for primary prophylaxis, breakthrough invasive fungal infection rates were approximately 3%[55].

Regarding non-azole mold prophylaxis, micafungin has been evaluated in a prospective observational study in patients with AML. In this study, of the 41 patients included, no invasive fungal infections were noted and only one patient experienced higher-grade toxicity[56]. However, there are few data at this time to recommend its routine use. Additionally, rezafungin, a novel echinocandin that is injected once per week, is currently being evaluated in a phase III trial to determine its efficacy in preventing invasive fungal infections in patients undergoing allogenic hematopoietic stem cell transplantation (NCT04368559). Further investigation is needed to understand the ideal agents for prophylaxis of invasive mold infections in this population, including the relative efficacy and safety of mold-active azoles and the utility of non-azole agents as well.

Treatment and future directions

Treatment for invasive mold infections depends on the specific mold involved and whether a patient is receiving prophylaxis. For invasive aspergillosis, voriconazole and isavuconazole are first-line agents, supported by a phase 3, randomized non-inferiority trial that compared their efficacies; of note, in this trial, isavuconazole was associated with fewer drug-related adverse events than voriconazole (Table 2)[57]. In cases where there is a contraindication to these two drugs, liposomal amphotericin B is recommended, and echinocandins can be considered as last-line agents[32]. Posaconazole has also been found to be non-inferior to voriconazole in a recent phase III randomized trial, but this finding is only valid until day 42 of follow up; further studies are needed to evaluate its role as a primary or alternative therapy in the treatment for invasive aspergillosis[58]. In the event of breakthrough infection while a patient is on azole-based mold-active prophylaxis, treatment should be initiated with an antifungal agent from a different class, generally liposomal amphotericin B[59].

For mucormycosis, in addition to potential surgical evaluation, initial recommend therapy is liposomal amphotericin B (Table 2). Isavuconazole and posaconazole can also be considered as second-line therapies[59]. However, to date, no randomized trials have been conducted to evaluate different treatment regimens for mucormycosis, largely due to the rarity of disease and emergent need for treatment. In a small, single-arm trial, researchers assessed the efficacy of isavuconazole for the treatment of mucormycosis and compared its efficacy with amphotericin B in a matched case-control analysis. In this study, isavuconazole showed activity against mucormycosis with similar efficacy to amphotericin B[60]. Finally, treatment of fusariosis can be more challenging due to higher rates of resistance compared to other invasive mold infections in this population, and generally relies on liposomal amphotericin B, voriconazole, or posaconazole[61].

In the modern era, novel antifungals are being further developed and evaluated due to limited treatment options and growing rates of antifungal resistance. More novel antifungals with anti-mold activity include olorfim and fosmanogepix (Table 2)[62]. In a limited interim analysis from an ongoing phase II trial (NCT03583164), Olorofim, a reversible DHODH enzyme inhibitor, was given to patients with invasive fungal infections with limited to no treatment options, and demonstrated at least a partial response in approximately one-third of

patients[63]. Fosmanogepix is a prodrug to manogepix, a GWT1 enzyme inhibitor, with preliminary phase II data showing approximately a 40% response rate in invasive mold infections in 20 enrolled patients (NCT04240886). In addition to these agents, alternative approaches have been utilized to augment immune response and aid in eradication of invasive fungal infections in neutropenic patients with hematologic malignancies. Namely, granulocyte transfusions have been evaluated in several contexts, including multiple randomized clinical trials, but results have been mixed. A recent Cochrane review by Estcourt et al. concluded that there is insufficient evidence to determine whether granulocyte transfusions impact all-cause mortality in patients with chemotherapy- or hematopoietic stem cell transplant- related neutropenia[64]. Overall, further investigation of novel antifungal agents and alternative approaches to augment response rate in the treatment of invasive mold infections will be imperative to improving clinical outcomes in this population.

Conclusion

Invasive mold infections represent an ongoing challenge in neutropenic patients with hematologic malignancies due to their morbidity and mortality, limited treatment options, and growing rates of resistance to existing antifungal agents. In the current era of caring for an increasing aging population with a higher prevalence of hematologic malignancies, the development of more effective strategies to diagnose, prevent, and treat these infections is of critical importance. In this review, we summarized the immunology that undergirds invasive mold infections in this population and the epidemiologic trends that have been observed globally. We discussed the challenges in diagnosing invasive mold infections, with a reliance on a combination of clinical, imaging, and microbiologic data and probabilistic models; we further emphasized ongoing efforts to develop non-invasive and diagnostically sound assays to better identify these infections, with ongoing efforts aimed at optimizing cell-free microbial DNA-based assays that have gained more widespread use. In addition to this, we discussed prophylactic strategies to prevent invasive mold infections, of which there are several, with current trials underway evaluating novel approaches using both established and investigational therapies. Finally, we laid out the current approaches to treatment of the most common invasive mold infections as well as novel, first-in-class therapies that are currently under investigation. Ongoing efforts to address invasive mold infections will be essential to the care of patients with hematologic malignancies.

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