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Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Common Fungal Infections in Patients With Leukemia

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H&O What is the mortality associated with fungal infections in patients with leukemia?

EW Acute myeloid leukemia (AML) constitutes the hematologic malignancy with the highest risk of associated fungal infections. Among patients with AML, the overall mortality rate from fungal infections was once 60% to 70%, but has improved in recent years to 20% to 30%. Throughout the literature, however, there is a wide range of factors with the potential to affect these numbers. Studies have shown that the mortality associated with invasive fungal infections in patients with AML undergoing induction therapy, autologous stem cell transplant, or allogeneic stem cell transplant may be as high as 40% to 60%, as compared with approximately 20% among patients treated with less-intensive or less-myelosuppressive therapy.

H&O What are the most common fungal infections in patients with acute leukemia?

EW It is interesting to note that, over time, the incidence of the most common fungal infections in patients with acute leukemia has changed. In the past, the most common fungal infection was invasive candidiasis arising from species of *Candida* (such as *Candida albicans*) that were fairly sensitive to fluconazole. Although invasive candidiasis is still frequently seen in patients with acute leukemia, the overall incidence has declined, and there has been a shift to the appearance of more therapy-resistant *Candida* species (such as *Candida glabrata*). Currently, the incidence of invasive mold infections with species such as *Aspergillus*, *Fusarium*, and *Mucorales* has been rising. Both of these trends can be directly attributable to the widespread adoption of prophylactic therapy with azole drugs for high-risk patients.

H&O What are the risk factors?

EW Multiple risk factors can predispose patients with acute leukemia to develop fungal infections. These can be roughly categorized into patient-related vs tumor-related factors.

Among the most important patient-related factors is the underlying fitness or functionality of the patient. Many studies have shown that older patients (≥60 years) with AML or myelodysplastic syndrome (MDS) with preexisting cytopenias have an increased risk of fungal infections because their innate immune system is weakened. Frail patients—again, who are more likely to be older—are thought to have a higher risk. Another risk factor is the type of therapy administered for the underlying leukemia. Numerous studies have shown a higher risk of fungal infections among patients with AML who are receiving intensive induction chemotherapy, autologous stem cell transplant, or allogeneic stem cell transplant as opposed to lower-dose, less-intensive chemotherapy regimens associated with shorter periods of myelosuppression. Intensive chemotherapy destroys the mucosal barrier, leading to mucositis, colitis, or gastritis, which may predispose patients to systemic fungal propagation and/or fungemia. Patients receiving other treatments that cause immunosuppression, such as prolonged high-dose corticosteroids, are also at higher risk.

There are other patient factors that can contribute to an increased risk of fungal infections. For example, patients with underlying organ dysfunction, particularly a history of pulmonary disease (eg, chronic obstructive pulmonary disease), or who are prior or current smokers are more likely to develop significant fungal pulmonary infections. Lastly, individuals living in certain warmer, more humid geographic regions; working in certain occupations (eg, construction); or residing in medical facilities lacking rooms filtered with high-efficiency particulate air (HEPA) may have increased exposure to or colonization with fungal pathogens located in the air or water.

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Leukemia-related factors may also play a role. Lower levels of fungal infections are observed in patients with MDS or acute lymphoblastic leukemia (ALL) than with AML. In any of these patients, a complete remission correlates with decreased fungal infections, presumably because of restoration of normal neutrophil counts and other immune cell function. Conversely, higher incidences of fungal infections are reported in patients with AML that is associated with unfavorable cytogenetic or molecular risk profiles and/or relapsed/refractory disease, partly because these patients are not in complete remission and may experience prolonged duration of myelosuppression.

H&O Are there ways to prevent fungal infections in these patients?

EW Yes, there are several approaches to decreasing the risk of fungal infections. Patients at high risk for fungal infections typically receive prophylaxis with an antimold azole drug. At my institution, we routinely prescribe posaconazole (Noxafil, Merck) for neutropenic patients with MDS or AML undergoing chemotherapy. The recommendation for posaconazole prophylaxis is based on positive results from a prior randomized clinical trial in which neutropenic patients with AML receiving induction chemotherapy were randomly assigned to receive either posaconazole vs fluconazole (or itraconazole) for prevention of invasive fungal infections. The results of this study demonstrated that patients receiving posaconazole had significantly fewer cases of invasive aspergillosis and significantly longer overall survival. Less commonly used treatments for prophylaxis include voriconazole (Vfend, Pfizer), micafungin sodium (Mycamine, Astellas), and inhaled or systemic amphotericin B. Another way to prevent or decrease fungal infections is to shorten the course of immunosuppressive therapy via administration of less-intensive chemotherapy regimens (eg, hypomethylating agents) when feasible and to add myeloid growth factors during prolonged neutropenic periods. We also try to address environmental factors. Patients reside in rooms with HEPA filters to limit exposure to air and water pathogens, particularly fungal pathogens.

H&O What do guidelines recommend for prevention of fungal infections?

EW The National Comprehensive Cancer Network has clear guidelines, most recently updated in February 2017. Patients with hematologic malignancies considered at intermediate or high risk of infection should routinely receive antifungal prophylaxis. For patients with AML or MDS who are neutropenic, the strongest recommendation (category 1) is to consider prophylaxis with posaconazole. There are lower-level recommendations (category 2B) for voriconazole, fluconazole, micafungin, and amphotericin B. For patients with ALL, who have a lower risk of invasive mold infections, there is a category 2B recommendation to consider use of fluconazole, micafungin, or amphotericin B. These agents should be continued prophylactically, ideally until resolution of the neutropenia. For patients who undergo an autologous stem cell transplant and develop mucositis, there is a category 1 recommendation for treatment with fluconazole or micafungin. These patients have a lower risk of fungal infection.

H&O What are the signs that a patient has a fungal infection?

EW The most common presentation of a leukemia patient with a fungal infection is a neutropenic fever of unexplained etiology. Typically, patients who develop a neutropenic fever will initially begin treatment with broad-spectrum antibiotics. A fever that persists without a clear source should prompt consideration of a systemic fungal infection, with the appropriate diagnostic workup. The second most common presentations of a fungal infection are pulmonary infections, such as pneumonia, and sinusitis. The third most common presentation is

disseminated infection, manifested commonly as skin lesions or soft tissue involvement, particularly in patients with systemic *Candida* infections or disseminated candidiasis. Lastly, infections may also be identified through a routine blood culture.

H&O Is a confirmed diagnosis needed before initiation of treatment?

EW There is some debate, but a confirmed diagnosis is not necessarily required. In high-risk patients, early initiation of antifungal therapy can be based on clinical suspicion, radiographic evidence, and/or laboratory tests, including a positive blood culture or fungal biomarker (such as serum galactomannan or β-glucan). In patients with more than 1 risk factor for fungal infection who are ill, empiric antifungal therapy may be administered based on clinical suspicion alone. Patients with few to no risk factors for fungal infection may benefit from a more measured approach, with delay of any definitive antifungal treatment until the diagnosis is confirmed by biopsy, culture, or serum biomarker profile.

H&O What kinds of treatments are available?

EW Several antifungal therapies are currently available for the treatment of fungal infections. If the fungal organism is known, then therapy typically is tailored to the specific species. Patients with candidiasis typically receive intravenous echinofungins. In contrast, individuals with confirmed or suspected invasive aspergillosis receive prolonged therapy with either voriconazole or amphotericin B, preferably the liposomal formulation. Among patients infected with mucor or any of the more rare fluvarium molds, we prefer to use amphotericin. Patients with mucor may also undergo surgical debridement for definitive therapy.

It must be kept in mind, however, that the antifungal agents are of varying efficacy. Their ability to eradicate infection and thereby reduce mortality greatly depends on the host's overall health and disease status. Efficacy is decreased among patients with refractory/relapsed leukemia, those who are unable to recover blood counts, those who require continuous therapy, those with organ dysfunction, those who are older, and those who are less fit.

H&O Can infections recur?

EW They can. For this reason, at our institute, we typically continue both prophylactic or definitive antifungal therapy in high-risk patients until resolution of the infection or, ideally, until recovery of the neutrophil count. We do not discontinue antifungal treatment prior to these endpoints because of the high risk that these infections will recur in the setting of a compromised hematopoietic system, with resulting poor outcomes.

H&O Do you have any other recommendations to prevent or manage fungal infections in patients with leukemia?

EW It is necessary to be clinically astute, to maintain a high level of suspicion, and to be aggressive in the management of fungal infections to avoid a high mortality rate. That being said, clinicians should also familiarize themselves with the most common toxicities associated with antifungal agents. They include kidney failure, hypersensitivity reactions following amphotericin administration, and toxicities of the liver, skin, and nervous system associated with azole therapies. In some patients, the financial cost of prolonged treatment with these agents may also be a concern.

Disclosure

Dr Wang has no relevant conflicts of interest to report.

Suggested Readings

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