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Management of Invasive Aspergillosis in Acute Myelogenous Leukemia

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H&O Why are patients with acute myelogenous leukemia (AML) at increased risk of developing invasive aspergillosis?

BM Approximately 10% of patients with AML develop invasive aspergillosis during aplasia that arises in the postinduction period or during administration of postremission therapy. There are several reasons why these patients are at increased risk of developing invasive aspergillosis. A significant number of patients with AML are exposed to spores in the environment. Inhalation of the spores can lead to a primary colonization. The disease process of AML includes a significant immunosuppressive state that increases the likelihood that a previously asymptomatic colonization will evolve to invasive aspergillosis.

The most common contributing factors are the severity and duration of neutropenia. Patients with AML have different degrees of bone marrow failure and suppression attributable to the disease itself. Some patients also develop neutrophil dysfunction, which increases the risk of invasive aspergillosis. Another major risk factor for prolonged duration of severe neutropenia is treatment with aggressive chemotherapy to address the underlying hematologic malignancy.

H&O Are there ways to prevent infection with invasive *Aspergillus*?

BM It is challenging to prevent infection. Many of these patients already have colonization of their bodies with the *Aspergillus* spores before diagnosis of AML. In patients who are not previously colonized, the utilization of rooms with laminar airflow systems may decrease the risk of contamination after the diagnosis. Protective barriers, such as masks, are commonly used to protect these patients to further reduce colonization and infection. The focus, however, is on monitoring for signs and symptoms of infection.

H&O What are the signs and symptoms of invasive aspergillosis?

BM In approximately 90% of patients with AML and invasive aspergillosis, the site of infection is the lungs. Disseminated invasive aspergillosis is relatively uncommon. Therefore, in most patients, the disease will manifest as pulmonary nodules or consolidations. The symptoms tend to be shortness of breath, cough, and chest discomfort.

H&O What is the potential impact of infection with invasive aspergillosis in a patient with AML?

BM The death rate associated with invasive aspergillosis has been significant. In the late 1980s, 40% to 50% of patients with invasive aspergillosis died from complications of the disease. Since the 1990s, the introduction of effective antifungal therapies, used as either prophylaxis or preemptive therapy, has significantly decreased aspergillosis-attributable mortality to between 20% and 30%.

Infection with *Aspergillus* can also interfere with the administration of chemotherapy and therefore negatively impact the prognosis of patients with AML. Treatment

may need to be delayed in patients with significant organ dysfunction or symptomatic or poorly controlled fungal infections, or in patients who undergo surgical procedures for debridement of aspergillomas.

H&O How are patients diagnosed?

BM There are several different diagnostic strategies. The initial workup of a patient with AML often includes use of nasopharyngeal and oropharyngeal swabs to identify prior exposure to *Aspergillus,* which could indicate high risk for the development of invasive aspergillosis throughout treatment. Some institutions may also perform rectal swabs at the time of admission to identify exposure.

During the treatment period, blood cultures are administered to patients who develop symptoms, most commonly fever or cough. These blood cultures occasionally lead to the diagnosis of invasive aspergillosis. Imaging studies, such as chest x-rays and computed tomography (CT) scans, will often reveal pulmonary nodules or infiltrate suggestive of invasive aspergillosis. A serum galactomannan assay is routinely performed in patients who have febrile neutropenia or when symptoms develop.

There are also tests for specific abnormalities. Patients occasionally present with disseminated disease in the brain or the sinuses. CT or magnetic resonance imaging of the sinuses and the brain are performed in these patients. When patients have cutaneous nodules, biopsies are frequently used for the diagnosis. Occasionally, fundoscopy examinations are used to identify retinal involvement of systemic aspergillosis. Among patients with pulmonary nodules, bronchoscopy with a bronchoalveolar lavage and transbronchial biopsy may lead to the diagnosis of invasive aspergillosis as well.

H&O What is the role of prophylaxis?

BM The US Food and Drug Administration approved the azole posaconazole (Noxafil, Merck) for the prophylaxis of invasive *Aspergillus* in patients at high risk of developing the infection. It is the only therapy approved for prophylaxis. High risk is generally defined as an absolute neutrophil count of 500 cells/mm^3 that is expected to persist for 7 days or more following remission-induction chemotherapy for newly diagnosed or relapsed AML.

Guidelines from the National Comprehensive Cancer Network provide 2 types of recommendations in regard to prophylaxis in this setting. There is a category 1 recommendation for the use of posaconazole until resolution of neutropenia. This recommendation is based on a randomized, multicenter clinical trial demonstrating that posaconazole prevented invasive fungal infections more effectively than fluconazole or itraconazole and also improved overall survival. There is a category 2B recommendation, which is less strong than category 1, that cites evidence suggesting a potential benefit for the use of voriconazole (Vfend, Pfizer), fluconazole, micafungin sodium (Mycamine, Astellas), or amphotericin B (AmBisome, Astellas) until resolution of neutropenia. A 2B recommendation does not mandate the use of these agents, but rather indicates that lower-level evidence led to an NCCN consensus that the intervention is appropriate.

Despite these recommendations, prophylaxis is not a universal practice at all institutions for several reasons. There is debate about whether the results of a single clinical trial should dictate clinical practice for a majority of patients. More importantly, there is the fear of breakthrough infections with specific species or subtypes of *Aspergillus* that are not sensitive to the prophylactic agent used.

H&O Can treatment of invasive aspergillosis be initiated before diagnosis is confirmed?

BM Empiric or preemptive therapies are started in patients who are at high risk or who develop symptoms. Unfortunately, the diagnosis of invasive aspergillosis is clinically confirmed in only a minority of patients with the disease. Antifungal therapy is often initiated based on the probable diagnosis, which means that the patient has signs and symptoms that are suggestive of invasive aspergillosis without true tissue confirmation of the infection.

In patients who have radiologic evidence or symptoms associated with aspergillosis or in those who are receiving therapy for neutropenic fever, there is a recommendation for the initiation of antifungal therapy between the fourth and seventh day of an unexplained fever that persists despite adequate treatment with antibiotics. Therefore, treatment is usually initiated based on a specific finding or it is given empirically in patients with persistent febrile neutropenia.

H&O How has the treatment of invasive aspergillosis evolved in the past few years?

BM Several different agents have been introduced. Approximately 20 years ago, amphotericin-B was the main treatment option. The azoles that were available, itraconazole and fluconazole, did not have great activity against *Aspergillus*. For patients with AML, the treatment algorithm for invasive aspergillosis has significantly changed over the past couple of decades, with the introduction of therapies such as liposomal amphotericin B; the echinocandins, such as caspofungin acetate (Cancidas, Merck); and the newer azoles, such as voriconazole and posaconazole. These new therapies are highly effective, with data suggesting that between 65% and 80% of patients will show some degree of clinical benefit.

H&O How do the azoles work?

BM Azoles are a commonly used antifungal therapy. They inhibit the enzyme sterol 14α-demethylase. This enzyme is involved in the formation of ergosterol, which is a lipid involved in the development of cell membranes for fungal elements. By inhibiting this enzyme, azoles reduce the production of ergosterol, which compromises the development of cell membranes in fungal elements.

H&O Should treatment be continued to prevent recurrence of infection?

BM It is critical to continue treatment as secondary prophylaxis for as long as the patient remains neutropenic or immunocompromised. Most guidelines state that subsequent treatment, often called secondary prophylaxis, should be used in patients who continue to receive therapy and are expected to experience further periods of neutropenia or immunosuppression. Those patients should receive therapy until they complete their chemotherapy regimens or until they complete immunosuppressive therapy after a bone marrow transplant.

Disclosure

Dr Medeiros has no real or apparent conflicts of interest to report.

Suggested Readings

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