Among the most significant complications a neutropenic patient can experience is an invasive fungal infection. In this issue of Oncology, Drs. Wingard and Leather thoroughly review the epidemiology, clinical presentation, and empiric treatment of these infections, particularly those associated with Candida and Aspergillus. They emphasize the need for better methods of identifying individuals at high-risk for invasive fungal infections because those individuals are more likely to benefit from antifungal prophylaxis or empiric therapy. The goal of such a targeted approach is to limit the amount of antifungal agents given, thereby decreasing the number of adverse effects and diminishing the selection of antifungal-resistant species.[1]

**Early Diagnosis Imperative**

For empiric therapy to be most effective, invasive fungal infections must be diagnosed early. Unfortunately, only half of patients with disseminated Candida infections have positive blood cultures. Moreover, surrogate laboratory markers for Candida and Aspergillus are either investigational or have limited predictive value; newer molecular-based techniques may be more applicable.[2,3] Consequently, recognizing the various risk factors listed in Table 4 of the Wingard and Leather article is essential.

Beyond those listed, there are several risk factors for invasive fungal infections unique to bone marrow transplant (BMT) recipients. These include allogeneic transplantation with donor mismatch, grade III and grade IV acute graft-vs-host disease, extensive chronic graft-vs-host disease, a donor seropositive for herpes simplex virus, veno-occlusive disease of the liver, recipient age greater than 40 years, and bacteremia during the aplastic phase of BMT.[4-8] However, beyond the level and duration of neutropenia, the particular contribution of any of these factors on the risk of invasive fungal infections is unclear.

A study from England recently showed the value of a targeted approach. They used bronchoalveolar lavage and high-resolution computed tomography scanning of the thorax to establish an early diagnosis of invasive pulmonary aspergillosis in patients with acute leukemia (a group at high-risk for invasive fungal infections). The overall incidence of proven or probable aspergillosis was 9%. By treating the suspected patients with a liposomal amphotericin B product, they increased the survival of infected patients from under 15% to 84%.[9] By combining risk factor assessment with diagnostic techniques in a high-risk population, the investigators were also able to decrease mortality. Nevertheless, this approach may not be as valuable for other neutropenic populations or for other types of fungal infections. Therein lies the complexity of empiric antifungal therapy.

**Antifungal Prophylaxis**

While we await advancements in the diagnosis of fungal infections, there remains a role for antifungal prophylaxis. In the era before antifungal prophylaxis was used, 11.4% of BMT recipients developed Candida infections within 3 months after transplant. Currently, that incidence is less than 4% when antifungal prophylaxis is used.[10]
Furthermore, the University of Washington detected a long-term survival advantage in allogeneic BMT recipients who received fluconazole (Diflucan) prophylaxis.[11] Patients who received prophylaxis had an 8-year survival of 45%, whereas those who did not receive prophylaxis had a survival of 28%. The authors postulated that this may "be associated with decreased gut graft-vs-host disease, a persistent protection against disseminated candidal infections and candidiasis-related death, resulting in an overall survival benefit in allogeneic BMT recipients."

Whether this prolonged benefit exists for other groups of patients, or even at other centers, remains to be determined. Nevertheless, the role of prophylaxis in allogeneic BMT recipients seems compelling. The only other triazole extensively studied for prophylaxis itraconazole (Sporanox). Although effective, it is not well tolerated.[12] In one study, 53% of participants discontinued itraconazole because of gastrointestinal side effects.[13] At this point, fluconazole remains the preferred agent for prophylaxis.

Resistant Strains

Despite the efficacy of such therapy, fluconazole-resistant non-*C. albicans* species have been problematic for oncology centers employing triazole prophylaxis throughout the 1990s. A disturbing increase in infections with fluconazole-resistant *C. albicans* is now at hand.[14,15] Furthermore, neutropenic patients are faced with a new opportunistic, resistant species, *C. dubliniensis*.[16] Increased gastrointestinal colonization with these resistant species can occur during triazole prophylaxis.[17]

Another concern is the observation that triazole prophylaxis may increase the risk of infection with other fungi, such as *Malassezia, Trichosporon, Blastoschizomyces, Rhodotorula, Saccharomyces, Clavispora, Hansenula,* and *Aspergillus*. Drs. Wingard and Leather downplay this effect, and given the infrequent occurrence of these superinfections, they suggest that empiric antifungal therapy be delayed in a febrile patient on prophylaxis without upper respiratory tract symptoms.

A more conservative approach might also require unremarkable dermatologic and neurologic examinations and chest radiography, in light of the frequent dissemination of fungi in the neutropenic patient.

Evidence-Based Approach

The crux of the Wingard and Leather article is found in Table 6. Distilled in this one table is a practical, mostly evidence-based approach to empiric antifungal therapy. By taking into account various factors such as the type of chemotherapy, the use of antifungal prophylaxis, and the presence of upper respiratory tract symptoms, a clinician can assess the risk for an invasive fungal infection and decide whether empiric antifungal therapy is warranted. It lacks a scoring or weighting system, but it does identify the known risk factors in the neutropenic patient.

The management recommendations in the right column, while reasonable, are broad guidelines that should be amended based on each center’s unique practice, patient mix, and epidemiology. Currently, antifungal choices are limited to the triazoles and the various preparations of amphotericin B, so once the decision to treat a suspected fungal infection is made, the choice of an antifungal agent is fairly straightforward. However, with the imminent availability of newer classes of antifungals, treatment options may need to be modified for the various pathogens, disease states, and risk factors. Frankly, this increased complexity will be most welcome.

References:


2. Chryssanthou E, Klingspor L, Tollemar J, et al: PCR and other non-culture methods for diagnosis of invasive Candida infections in allogeneic bone marrow and solid organ transplant recipients. Mycoses...


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