Invasive fungal infection (IFI) prevention and management in hematopoietic cell transplantation (HCT)

John R. Wingard
University of Florida College of Medicine

Candida and Aspergillus are the chief fungal pathogens after HCT. Most Candida IFIs occur during the first month after HCT with prolonged neutropenia, use of central venous catheters, and antibiotics as major risk factors. Use of azole or echinocandin antifungal prophylaxis has dramatically reduced the threat from Candida. Although antifungal resistance in non-albicans Candida species is a growing problem in other patient groups, this remains infrequent in HCT patients.

Invasive Aspergillus (IA) can also occur early after transplant, usually as recurrences of prior IA, but most Aspergillus IFIs occur during the second and third month after transplant. The major risk factors are graft versus host disease (GVHD) and use of prolonged high-dose corticosteroids. Historically, mortality rates have been high.

Over the past decade, several practice changes have led to better IA treatment outcomes: an improved understanding of IA risk factors, an emphasis on heightened vigilance in high-risk patients, advances in IA diagnostics, aggressive use in radiologic and biomarkers evaluations to facilitate early recognition, adoption of the practice of prompt initiation of antifungal therapy, and the introduction of new therapeutics. However, because of persistent morbidity and mortality concerns, there has been a growing emphasis on prevention, following on the success of fluconazole prophylaxis to prevent Candida IFIs.

Multiple IA prophylaxis studies have been performed. Itraconazole prophylaxis has been shown to be effective but bioavailability and tolerance concerns are limitations. Amphotericin preparations are also active and several studies have shown efficacy, but toxicity and the need for parenteral administration have made this suboptimal to administer over the prolonged risk period. Several trials have tested lipid amphotericin B as adjunctive treatment with promising results and one randomized prophylaxis trial found that repeated inhalations of liposomal amphotericin B resulted in a protective effect with a reduction in IA in patients treated for acute myelogenous leukemia (AML). This has not yet been evaluated in HCT patients.

In recent years IA prophylaxis studies have focused on the mold-active azoles, posaconazole and voriconazole. Posaconazole prophylaxis was found to be associated with a trend to fewer IFIs of all types and fewer IAs in HCT patients with GVHD receiving corticosteroids. However, important to note, the benefit was confined to the subgroup of patients with positive galactomannan testing (GM) at the start of the study drug. Two large randomized trials examined voriconazole prophylaxis in HCT patients. In one trial voriconazole was compared to fluconazole. Both voriconazole and fluconazole were well tolerated and had similar rates of survival free of IFI at 6 months. Risk factors for IFIs were GVHD, older age, and an underlying disease of AML. In the subgroup of patients transplanted for AML, there were fewer IFIs and better fungal-free survival with voriconazole than with fluconazole prophylaxis. In another trial, voriconazole was compared with itraconazole. There were similar rates of IFIs and survival, but voriconazole was better tolerated than itraconazole.

Several studies suggest the use of routine serial serum GM screening can identify incipient IA and twice weekly screening can be used to prompt evaluation with CT scans, bronchoscopic evaluation when indicated, and early initiation of presumptive antifungal therapy. This strategy of screening with early therapy when IA is suspected is sometimes known as ‘pre-emptive’ therapy. Several trials have evaluated this approach with promising results and this has been advocated by some experts as a viable alternative to universal prophylaxis for mold IFIs.

Studies also suggest that GM testing of bronchoalveolar fluid samples is very sensitive and specific in identifying pneumonias due to Aspergillus. In addition to the GM and beta-glucan biomarker tests, Aspergillus PCRAs are now available and studies show the promise of molecular testing to identify IA even earlier.

Recent genetic studies of human variants of immune response genes and pattern recognition molecules on cell membranes indicate that certain host genetic variants can identify individual patients at especially high risk for IA. Such studies are expanding our understanding of risk factors and open the possibility for designing individualized approaches to prevention and treatment. It is easy to envision future approaches to minimizing morbidity and mortality from IA that will incorporate both knowledge of host genetic susceptibility profiles along with testing using highly sensitive fungal screening tests, and the use of antifungals used as prophylaxis in some patients (those at highest risk) and as early therapy in others at lower risk.