Are respiratory complications more likely in patients with pulmonary aspergillosis treated with echinocandins in the setting of neutrophil influx?

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There is controversy about the usefulness of granulocyte transfusions (GTX) for the treatment of invasive pulmonary aspergillosis (IPA). Moreover, this strategy is associated with frequently severe respiratory complications. As antifungal combinations with a cell wall acting echinocandins is common scenario for treatment of breakthrough IPA to Aspergillus-activeazole prophylaxis, we hypothesize that respiratory complications following GTX would be expected to be increasingly frequent. Echinocandins uncover immunogenic epitopes in Aspergillus cell wall, and influx of neutrophils into tissue harboring echinocandin-exposed Aspergillus could result in diffuse inflammation. If this hypothesis is correct, immune reconstitution inflammatory syndrome (IRIS) associated with neutrophil recovery should be also more common in cases of IPA treated with echinocandins compared with other agents (triazoles, liposomal amphotericin B products) that do not induce immune activation of damaged Aspergillus.

In the treatment of profoundly neutropenic patients with severe bacterial or fungal infections, few areas have generated as much controversy as the use of granulocyte transfusions (GTX).1 This strategy was conceived following the success of platelet transfusions for reducing bleeding complications in severely thrombocytopenic cancer patients in the early 1960s.2 However, despite its theoretical appeal, conclusive evidence of a benefit with adjunctive GTX in the treatment of invasive fungal infections, particularly for invasive molds such as aspergillosis,1 remain limited in the current era of improved diagnostics and therapeutic options.3 Even contemporary trials that utilized improved technologies for WBC procurement, storage, and mobilization (i.e., G-CSF elicited) and higher granulocyte doses have failed to show a survival benefit.4

GTX transfusions can unequivocally improve neutrophil counts, but a magic ANC dosing threshold associated with improved clinical response to antifungal therapy remains elusive.1 Furthermore, concerns about various adverse reactions persist. Perhaps the most worrisome is the issue of severe pulmonary complications following GTX. The frequency of such complication has ranged broadly from 10% to 53% in recent studies. The wide range in reported pulmonary events can be explained, in part, by different GTX administration practices (frequency, dose, pre-medications), how pulmonary complications were diagnosed or documented (always difficult retrospectively), and differences in indication for GTX.1,5,6 For example, compared with febrile neutropenia population as a whole, patients with established IPA are often present at later stages of relapsing underlying malignancy, frequently have received more transfusions of blood products, thereby increasing the risk for alloimmunization and volume overload. Also, these patients could have a greater probability of undiagnosed pulmonary co-infections that “flare” with the GTX.

We would like to offer another possible explanation on pulmonary complications remain problematic with GTX. In preclinical experiments, exposure of Aspergillus to echinocandins alters the fungal cell wall and uncovers immunogenic epitopes, resulting in increased inflammatory responses.7,8 If this is also true in patients, influx of neutrophils into tissue harboring echinocandin-exposed Aspergillus could theoretically result in diffuse inflammation and tissue damage (Fig. 1) and severe bleeding from necrotizing IRIS reactions surrounding proximal pulmonary vessels. Although there is no experimental data, there is little theoretical reason to believe that differences exist among the echinocandins in regards to increased pro-inflammatory responses in the setting of neutrophil influx in fungal lung lesions. Because combination therapy with echinocandins and liposomal amphotericin B are frequently considered in severe cases of aspergillosis that have failed triazole prophylaxis, the combination of two “inflammation” eliciting drugs may intensify this phenomenon in select patients. Amphotericin B, directly activate immune cells through microbial pattern recognition receptors (Toll-like receptor 2, CD14), causing the release of proinflammatory cytokines (TNF-α, IL-6, IL-1RA, IL-1β), chemokines (IL-8, MCP-1, MIP-1β), nitric oxide, and prostaglandins.9,10 Older studies have suggested that co-administration of amphotericin B–deoxycholate with GTX results in high rates of severe pulmonary reactions.9-12 This phenomenon has not been replicated nor observed as frequently, however, with the lipid...
amphotericin B formulations, perhaps due to immunomodulatory properties of lipid formulations of amphotericin B. In addition, antifungal-induced immune activation of damaged Aspergillus could potentiate the vasculopathy, endothelial, and platelet activation associated with fungal invasion of the lungs (Fig. 1). The recently completed phase III NHLBI-sponsored randomized controlled study (RING trial, NCT00627393) hopefully will address some of the controversies of the impact of GTX in established pulmonary aspergillosis in neutropenic patients to make some meaningful comparisons. Should that be the case, we would like to suggest that carefully factoring the influence of prior or concomitant antifungals, particularly echinocandin therapy would be important for the analysis. This information could complement the careful plan to evaluate alloimmunization (anti-HLA antibodies) and other GTX-related serious adverse effects. Finally, the “outliers” with severe lung reactions secondary to GTX in the setting of an established lung infection could have an immunogenic component for their susceptibility. Emerging research suggests a tissue specificity of organ damage and clearance of fungi and other pathogens can be influenced by genetic lesions in specific chemokines or cytokines. We believe that a tissue (blood, bronchoalveolar lavage) registry along with compilation of well documented cases of severe GTX reactions in the setting of pulmonary aspergillosis in the context of different antifungal treatments, especially the echinocandins, would be of interest. A carefully conducted comparative study on whether the IRIS associated with neutrophil recovery is more common in cases of pulmonary aspergillosis treated with echinocandins compared with other agents (triazoles, liposomal amphotericin B products) could be of interest and strengthen the current hypothesis (Fig. 1). Finally, our hypothesis should be testable experimentally in the mouse model of invasive pulmonary aspergillosis. Specifically, one could compare (survival, fungal burden, immune profiling in serum and BAL, immunopathology) in neutropenic mice infected with Aspergillus that were given subtherapeutic doses of an echinocandin vs. subtherapeutic doses of a triazole (as a control) vs. no treatment, both during neutropenia and at the time of neutrophil recovery.

Disclosure of Potential Conflicts of Interest

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