Progression of *Pneumocystis jiroveci* Pneumonia in Patients Receiving Echinocandin Therapy

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Echinocandins are a novel class of antifungal drugs that target β (1, 3)-D-glucan synthesis. Animal studies have shown that these agents have activity against *Pneumocystis jiroveci* infection; however, clinical data are lacking. We reviewed all cases of proven *P. jiroveci* pneumonia (PCP) in non–human immunodeficiency virus-infected patients at our hospital over a 5 year period (2001–2005). Two patients received conventional PCP treatment and concomitant use of echinocandins for presumed invasive aspergillus. In both cases, PCP progressed, and the patient died. The use of echinocandins in the prevention or treatment of PCP cannot be recommended without evidence to support their effectiveness.

*Pneumocystis jiroveci* pneumonia (PCP) remains an important cause of morbidity and mortality in immunocompromised patients. Up to one-third of patients with PCP are intolerant of or fail to respond to treatment with trimethoprim-sulfamethoxazole [1–3]. Second-line agents, such as pentamidine or clindamycin-primaquine, are also associated with significant toxicity [4]. Echinocandins (e.g., caspofungin, micafungin, and anidulafungin) are a new class of antifungal drugs that target β (1, 3)-D-glucan synthesis. These agents are active against *P. jiroveci*, which contain β (1,3)-D-glucan in their cell walls, and have been effective in animal models of PCP [5–10]. However, only a few case reports have described the use of echinocandins to treat PCP in humans [11, 12], and no cases of treatment failure have been published.

In January 2001, caspofungin became the first echinocandin to be approved by the US Food and Drug Administration (FDA), and it is now licensed for the treatment of invasive infections caused by *Candida* species and *Aspergillus* species. Since then, at our institution (Memorial Sloan-Kettering Cancer Center [MSKCC]; New York, NY), patients who received echinocandin therapy for prevention or treatment of a possible, probable, or proven fungal infection also received an agent with possible activity against PCP. We reviewed patient records from all cases of PCP at MSKCC between January 2001 and December 2005 to further define the role of echinocandins in the management of PCP.

Methods. MSKCC is a 432-bed tertiary cancer care center in New York City, with approximately 19,000 hospital admissions each year. All patients assigned an *International Classification of Diseases, 9th Revision* (ICD-9) diagnostic code for PCP between January 2001 and December 2005 at MSKCC were identified from patient records. Bronchoscopy, microbiology, cytology, pathology, and autopsy records were reviewed to identify additional patients. Patients with known HIV infection were excluded.

Specimens obtained by bronchoalveolar lavage (BAL) are routinely submitted both to the microbiology laboratory for toluidine blue staining and to the cytology laboratory for Gram-Weigert staining. Lung biopsy specimens were examined in the pathology laboratory using methenamine silver staining. A case of PCP was defined as an instance of morphologic evidence of *P. jiroveci* by toluidine blue, Gram-Weigert, or methenamine silver stain in a respiratory or biopsy specimen.

Patient charts were reviewed to identify patient demographic characteristics, underlying conditions, prior chemotherapy and/or radiation therapy, corticosteroid use, PCP prophylaxis, echinocandin use, and outcomes. The study was reviewed and approved by the MSKCC Institutional Review Board.

Results. During the 5-year interval, 22 patients received a diagnosis of PCP. Among these, 2 patients were identified who had proven PCP and who had received echinocandin therapy for treatment of *Aspergillus* species infection. Both patients died of respiratory failure despite 30 and 18 days of echinocandin therapy standard anti-*Pneumocystis* therapy.

Patient 1 was a 42-year-old woman with acute T-cell lymphocytic leukemia who was admitted to the hospital with fever, tumor lysis syndrome, and interstitial lung infiltrates 1 month after receiving induction chemotherapy. She was empirically treated with trimethoprim-sulfamethoxazole for PCP. Bronchoscopy performed 2 days later was diagnostic for PCP. Because of continued fever, micafungin therapy was initiated 1
week later to treat a possible fungal infection. A second bronchoscopy performed 9 days later again revealed PCP. The patient died 41 days after PCP diagnosis; she had received 43 days of anti-\textit{Pneumocystis} treatment with various agents and 30 days of micafungin. An autopsy revealed T-cell lymphocytic stem cell transplantation that was complicated by chronic graft-versus-host disease, multiple episodes of cytomegalovirus reactivation, and catheter-associated bloodstream infection. He received aerosolized pentamidine therapy every 2 weeks for PCP prophylaxis. On day 277 after hematopoietic stem cell transplantation, a cavitary pulmonary nodule was observed on CT scan. Caspofungin therapy was added on the basis of suspicion of invasive aspergillosis. Worsening respiratory symptoms and progression of interstitial infiltrates on CT scan resulted in the performance of a bronchoscopy 9 days after the addition of caspofungin therapy that revealed \textit{Pneumocystis} cysts. Intravenous pentamidine therapy was added. The patient died 9 days later from progressive respiratory failure presumed to be related to PCP, although no autopsy was performed.

\textbf{Discussion.} Echinocandins are active against a wide variety of fungi in vitro and in vivo [13]. The class was initially developed as a novel therapy for PCP. With the incidence of PCP in patients with HIV infection decreasing as a secondary result of widespread prophylaxis and the introduction of HAART, the activity of echinocandins against traditional fungi was noted, and this indication was pursued [14]. In general, echinocandins are very well tolerated and have minimal drug-drug interactions. Thus, they are attractive alternatives to currently available therapies for the treatment of invasive fungi.

Several reports have described high rates of attributable mortality among patients with cancer who have developed PCP [15]. Exposure to new chemotherapeutic and immunomodulatory agents is now responsible for a growing proportion of patients without HIV infection who develop PCP. In the 1990s, reports were published of PCP developing in patients who received purine analogues, particularly fludarabine [16]. More recently, PCP has been observed in patients receiving temozolomide (an oral alkylating agent used in the treatment of brain tumors and melanoma that is associated with significant CD4 cell lymphopenia [17]) and in patients treated with infliximab (an anti-TNF-\(\alpha\)-neutralizing antibody administered for such conditions as rheumatoid arthritis [18]). As additional novel agents become available to treat more conditions, PCP and other opportunistic infections that exploit profound T cell defects can be expected.

No role has been established for the use of echinocandins in the management of PCP. At least 2 patients have been described who received echinocandins as part of the successful management of PCP. In both cases, however, the benefit conferred from echinocandin treatment is questionable. Annaloro et al. [11] described a 45-year-old man who was treated for proven PCP with trimethoprim-sulfamethoxazole for 2 weeks. His pulmonary infiltrates, however, persisted. No follow-up bronchoscopy was performed at that time to further assess the response. Despite the infiltrates, he then received an allogeneic hematopoietic stem cell transplantation. In the post-transplantation period, he received 6 weeks of caspofungin therapy. His pulmonary infiltrates resolved, which the authors took as evidence of caspofungin activity against \textit{Pneumocystis}. Beltz et al. [12] described a pediatric patient with acute lymphoblastic leukemia who responded to treatment of PCP with concurrent caspofungin and trimethoprim-sulfamethoxazole. Thus, the specific contribution of the echinocandin could not be assessed.

In contrast to these reports, both of our patients who received an echinocandin eventually died of progressive respiratory failure. The first patient, for whom 43 days of conventional PCP treatment failed, also did not respond to 30 days of micafungin. Her progressive clinical deterioration—despite both conventional anti-\textit{Pneumocystis} therapy and administration of an echinocandin—suggests either a more aggressive infection or a more immunocompromised host. Prophylaxis with aerosolized pentamidine failed for the second patient and, despite receiving 18 days of echinocandin therapy and 9 days of standard concurrent anti-\textit{Pneumocystis} therapy, he died of progressive respiratory failure believed, but not proven, to be due to PCP.

Several factors, including the high morbidity and mortality of PCP, the significant cost of echinocandins, and the lack of an oral echinocandin formulation, make it difficult to systematically assess the utility of echinocandins in the prevention and treatment of PCP in patients with cancer. The problem is further compounded by the lack of an approved serologic or DNA-based method for diagnosis. Laboratory tests are mostly based on microscopy and may be <70% sensitive for the diagnosis of PCP [19], although a more sensitive monoclonal antibody test is available [20].

The pedigree of the echinocandin class of antimicrobials, in addition to their safety and improving pharmacokinetic profile, may tempt clinicians to consider using them as prophylaxis against or treatment for PCP. However, our cases—which demonstrate progressive disease—as well as the lack of compelling evidence in published reports to support claims of efficacy, strongly argue against the use of echinocandins in PCP prophylaxis or treatment.

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References