Progressive Disseminated Aspergillosis in a Bone Marrow Transplant Recipient: Response with a High-Dose Lipid Formulation of Amphotericin B

Dimitrios P. Kontoyiannis,1 Borje S. Andersson,2 Russell E. Lewis,1,3 and Issam I. Raad1

Departments of 1Internal Medicine Specialties and 2Blood and Marrow Transplantation, The University of Texas M. D. Anderson Cancer Center, and 3Department of Clinical Sciences and Administration, College of Pharmacy, University of Houston, Houston

We present a case of progressive disseminated aspergillosis that involved multiple sites in a bone marrow transplant recipient with severe, chronic graft-versus-host disease. The patient failed to respond to treatment with a conventional dosage of a lipid formulation of amphotericin B (lifoAmB; 5 mg/kg/day) given alone or in combination with itraconazole, and he responded only to an aggressive strategy that included a very high dosage of lifoAmB (15 mg/kg/day) given in combination with itraconazole as well as a rapid reduction in immunosuppression. Despite the patient’s abnormal baseline kidney function, the very high doses of lifoAmB were well tolerated and did not result in additional renal toxicity.

Disseminated invasive aspergillosis (IA) typically is a fatal disease in patients with advanced immunosuppression and severe graft-versus-host disease (GVHD) who receive a bone marrow transplant [1]. In this report, we present a case of progressive disseminated IA with multiple-organ involvement that responded to very high doses of a lipid formulation of amphotericin B (lifoAmB) and a reduction in immunosuppression.

A 23-year-old man who had a history of refractory Hodgkin’s disease received a bone marrow transplant from a matched, unrelated donor on 21 August 1997. He underwent engraftment on day 14 after transplantation, and his neutrophil count has remained adequate since that time. His posttransplantation progress was complicated by severe, chronic GVHD that required prolonged administration of high-dosage methylprednisolone (MP; 40 mg/day) and tacrolimus (FK 506), which subsequently resulted in severe immunosuppression and debilitation. The patient had multiple opportunistic infections, including septicemias caused by methicillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa, and vancomycin-resistant Enterococcus species; pneumonia caused by Nocardia asteroides; recurrent infection with varicella-zoster virus; recurrent retinitis caused by cytomegalovirus; and keratitis caused by herpes simplex virus.

On 31 July 1998 (day 330 after transplantation), the patient began receiving iv lifoAmB (AmBisome; Fujisawa Healthcare) for documented pulmonary IA caused by Aspergillus fumigatus. He initially received the drug in a dosage of 5 mg/kg/day given for 21 days; because of a rising serum creatinine level (which increased from a baseline level of 0.9 mg/dL in June 1998 to 2 mg/dL on 21 August 1998), he then began receiving the drug every other day. He also continued to receive long-term therapy with trimethoprim-sulfamethoxazole (TMP-SMZ) and minocycline for nocardiosis. Overall, the patient was clinically stable; however, on 10 October 1998 (day 426 after transplantation), he had a new onset of fever (temperature, 38°C [while he was receiving MP, 32 mg/day]), chills, malaise, and abdominal pain associated with a new left lower lobe infiltrate. A blood sample was obtained by use of a central venous catheter and was cultured; the culture yielded A. fumigatus. On 13 October 1998, the patient’s lifoAmB treatment schedule was changed to daily treatment with 5 mg/kg/day. On 23 October 1998, 2 mildly painful subcutaneous nodules developed in the patient’s anterior chest wall. Fine-needle aspiration (FNA) of one of the nodules showed numerous invading fungal hyphae, a finding consistent with a diagnosis of IA; however, the culture result was negative. In addition, the results of the patient’s liver function tests (in particular, measurement of the alkaline phosphatase level) and findings on a CT scan of his abdomen showing scattered, focal, hypoenhancing lesions in the liver and a focal lesion in the right kidney were consistent with disseminated fungal infection or focal involvement by lymphoma. A liver biopsy was performed, but its results were not diagnostic. After disseminated aspergillosis (of the blood, lungs, subcutaneous tissue, and, possibly, the liver) was diagnosed, the lifoAmB dosage was increased to 7.5 mg/kg/day on 23 October 1998, despite the presence of an elevated serum creatinine level of 1.5 mg/dL. In addition, the dose of steroids given to the patient was rapidly tapered. The central venous catheter was removed, but a culture...

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Reprints or correspondence: Dr. Dimitrios P. Kontoyiannis, Dept. of Internal Medicine Specialties, Box 47, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030 (dkontoyi@notes.mdacc.tmc.edu).

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of a sample from the catheter tip was negative for *Aspergillus* species. Multiple repeat blood cultures were negative for *Aspergillus* species, and a transesophageal echocardiogram did not show vegetations.

Despite the changes in treatment, new subcutaneous nodules continued to develop. FNA was repeated, and it showed that one of the subcutaneous nodules had numerous invading fungal hyphae, a finding consistent with IA. On 27 October 1998, administration of lifoAmB was discontinued because of progressive aspergillosis; the patient then began receiving the investigational echinocandin MK-0991, 50 mg/day. On 30 October 1998, the patient developed increasingly severe back pain and had marked tenderness on percussion of the thoracic vertebrae. MRI of the spine showed findings consistent with diffuse diskitis plus erosive osteomyelitis at the T8-10 disk. CT-guided FNA of the T8-9 disk showed invading fungal hyphae, consistent with IA. In addition, cultures again yielded *A. fumigatus*.

On 11 November 1998, the patient began receiving subcutaneous granulocyte colony-stimulating factor (G-CSF) every day and IFN-γ, 50 µg/m², 3 times per week. After 37 days of receiving treatment with the investigational echinocandin MK-0991, the patient’s condition slowly deteriorated. He experienced increasing temperature, new skin lesions, increasing severity of back pain, and new pleuritic chest pain and friction rub. Imaging studies showed increasing numbers of spinal, pulmonary, liver, and kidney focal lesions. The patient also complained about increasingly blurred vision and pain in the left eye. Ophthalmologic examination revealed a left vitritis, and corneal scrapings showed hyphae of *Aspergillus* species. The patient then began receiving topical natamycin.

Treatment with the investigational echinocandin was discontinued on 2 December 1998, and administration of high-dosage lifoAmB (7.5 mg/kg/day for a serum creatinine level of 1.2 mg/dL) plus oral itraconazole (400 mg/day) was initiated. In addition, at the same time, administration of granulocyte-macrophage CSF (GM-CSF; 250 mg given every other day) was substituted for administration of G-CSF. Because of further clinical deterioration and the refractoriness of the disseminated IA to the aforementioned regimen, and despite the fact that the patient had abnormal baseline renal function (serum creatinine level, 1.3–1.8 mg/dL), the lifoAmB dosage was rapidly escalated to 10 mg/kg/day (given on 10 December 1998), 12.5 mg/kg/day (given on 12 December 1998), and then 15 mg/kg/day (given on 13 December 1998).

The patient’s condition slowly improved while he received the aforementioned regimen, with resolution of fever, skin lesions, and chest pain. The patient’s back pain slowly resolved, but repeated MRI scans of the spine (obtained 8 December 1998) showed little change in the appearance of the T8-10 diskitis and osteomyelitis. However, repeated CT scans of the chest and abdomen (obtained 21 December 1998) showed significant regression of the pulmonary and liver lesions. In addition, successive ophthalmologic evaluations showed gradual resolution of the vitritis. On 21 January 1999, the lifoAmB dosage was changed to 15 mg/kg given every other day, as a result of a slowly rising creatinine level (2.1 mg/dL).

The patient stopped receiving FK 506 and all steroids on 3 March 1999. He also stopped receiving IFN-γ and GM-CSF on 24 March 1999. Because of the patient’s marked clinical improvement and the chronic elevation of his serum creatinine level, lifoAmB treatment was finally discontinued on 24 September 1999, after 10 months of therapy. The most recent CT scans of the chest (obtained 2 June 2000) and abdomen (obtained 10 October 1999) and the most recent MRI scan of the spine (obtained 17 March 2000) all showed significant improvement of the radiologic abnormalities. The patient continued receiving itraconazole until 24 November 1999. He has been without any clinical evidence of GVHD or IA since 16 June 2000 (7 months after the discontinuation of all antifungal treatment). His serum creatinine level remains elevated at 1.9 mg/dL.

Among patients with severe GVHD who have undergone bone marrow transplantation, the mortality rate associated with disseminated IA is nearly 100% [1]. Our report outlines several interesting features of a particular case of IA. First, the case of IA in our patient involved multiple sites and featured a rather unusual organ distribution and a positive blood culture result. True aspergillemia is exceedingly rare, even among patients who are at highest risk for IA [2]. Second, both lifoAmB, which was given in a conventional dosage (5.0–7.5 mg/kg/day), and the investigational echinocandin MK-0991, which was given as salvage monotherapy, failed to control the infection. In contrast, the patient responded to an aggressive strategy that included very high doses of lifoAmB in combination with itraconazole and a rapid reduction in immunosuppression. Even though the use of combination therapy with itraconazole and amphotericin B (AmB) in selected patients with refractory IA remains controversial [3], it seems that our patient responded only after administration of very high doses of lifoAmB was begun. Finally, despite the patient’s abnormal baseline kidney function, the very high doses of lifoAmB that were used were well tolerated and did not result in additional toxicity.

The response of IA at all sites involved could be a reflection of (1) the favorable pharmacokinetics of lifoAmB in sites such as the liver, lungs, and kidneys, and (2) the delivery of higher doses of the drug to tissues that are difficult to penetrate, such as bone and the eyes [4]. Walsh et al. [5] recently reported their experience from phase I and II studies of the use of high-dose lifoAmB for the treatment of patients infected with *Aspergillus* species or other filamentous fungi. Of interest, lifoAmB exhibited saturation kinetics at dosages of >7.5 mg/kg/day, which suggests that there are dose-related changes in the dis-
tribution and clearance of lifoAmB in association with increased serum concentrations of the drug. However, despite their observation of high serum concentrations of lifoAmB, the authors noted no association between dose and increases in renal dysfunction or infusion-related reactions. The pharmacodynamic properties of AmB also support escalation of the lifoAmB dose given to patients with invasive mycoses. Conventional AmB and lifoAmB have been shown to exhibit concentration-dependent pharmacodynamics against Candida species in vivo [6, 7]. Therefore, the antifungal efficacy of AmB may be enhanced by maximization of the AmB concentrations (maximum plasma concentration:MIC or area under-the curve:MIC) at the site(s) of infection. Finally, the existing evidence from animal models of invasive candidiasis [6, 7] and the early clinical experience regarding the safety and the efficacy of lifoAmB used at higher doses for refractory IA [5] both suggest that this strategy deserves further study.

References