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A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis.

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BACKGROUND: Cryptococcosis is a life-threatening infection among patients with human immunodeficientcy virus (HIV) infection. Therapeutic options for the treatment of central nervous system cryptococcosis are limited, especially in resource-limited settings.
METHODS: We conducted a randomized, open-label, phase II trial in Thailand and the United States that compared the safety and efficacy of intravenous amphotericin B deoxycholate (AmB) 0.7 mg/kg (the standard therapy) with that of AmB 0.7 mg/kg plus fluconazole 400 mg (the low-dosage combination) or AmB 0.7 mg/kg plus fluconazole 800 mg (the high-dosage combination) administered daily for 14 days, followed by fluconazole alone at the randomized dosage (400 or 800 mg per day) for 56 days. The primary safety end point was the number of severe or life-threatening treatment-related toxicities; the primary efficacy end point was a composite of survival, neurologic stability, and negative cerebrospinal fluid culture results after 14 days of therapy.
RESULTS: A total of 143 patients were enrolled. There were no differences in treatment-related toxicities among the 3 arms. Toxicity was predictable and was most often related to AmB, and it included electrolyte abnormalities, anemia, nephrotoxicity, and infusion-related events. At day 14, 41%, 27%, and 54% of patients in the standard therapy, low-dosage combination, and high-dosage combination therapy arms, respectively, demonstrated successful outcomes. A trend towards better outcomes in the combination therapy arms was seen at days 42 and 70.
CONCLUSIONS: AmB plus fluconazole administered at a dosage of 800 mg for 14 days, followed by fluconazole administered at a dosage of 800 mg daily for 56 days, is well-tolerated and efficacious among HIV-positive patients with central nervous system cryptococcosis. These results have significant treatment implications and should be validated in a randomized phase III trial.

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