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High-dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV-infected patients: a randomized trial.

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Backgound: The standard therapy for human immunodeficiency virus (HIV)-associated cryptococcal meningitis of amphotericin B (AmB; 0.7 mg/kg per day) plus flucytosine frequently takes >2 weeks to sterilize the cerebral spinal fluid, and acute mortality remains high. A dosage range for AmB of 0.7-1 mg/kg per day is noted in current guidelines, but there are no data comparing 0.7 mg/kg per day with 1 mg/kg per day. Methods: Sixty-four HIV-seropositive, antiretroviral therapy-naive patients in Cape Town, South Africa, who experienced their first episode of cryptococcal meningitis during the period May 2005-June 2006 were randomized to receive either (1) AmB, 0.7 mg/kg per day, plus flucytosine, 25 mg/kg 4 times per day (group 1; 30 patients); or (2) AmB, 1 mg/kg per day, plus flucytosine, 25 mg/kg 4 times per day (group 2; 34 patients). Regimens were given for 2 weeks, followed by treatment with oral fluconazole. The primary outcome measure was early fungicidal activity, as determined by results of serial, quantitative cerebral spinal fluid cryptococcal cultures. Secondary outcome measures were safety and mortality. The median duration of follow-up was 1 year. Results: Early fungicidal activity was significantly greater for group 2 than for group 1 (mean +/- SD, -0.56 +/- 0.24 vs. -0.45 +/- 0.16 log cfu/mL of cerebral spinal fluid per day; P = .02). The incidence of renal impairment did not significantly differ between the 2 groups. Anemia was associated with female sex and, less strongly, with membership in group 2. Renal impairment and anemia reversed after the regimen was switched to fluconazole. Two- and 10-week mortality rates were 6% and 24%, respectively, with no difference between groups. Conclusions: Amphotericin B, 1 mg/kg per day, plus flucytosine is more rapidly fungicidal than is standard-dose Amphotericin B plus flucytosine. Because of its size, this study provides limited data on any difference in toxicity between the regimens, but toxicities were manageable and reversible. Clinical Trials Registration Number: ISRCTN68133435 (http://www.controlled-trials.com).