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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(See the editorial commentary by Harrison on pages 1784–6)

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.

Clinical trials registration. This clinical trial is registered in the National Library of Medicine's registry (http://www.clinicaltrials.gov) under the registration number NCT00145249.

Cryptococcosis is a serious infection in patients with advanced human immunodeficiency virus (HIV) infection. A recent study suggests that there are ~1 million new cases and at least 500,000 deaths annually worldwide due to HIV-associated cryptococcosis [1]. The vast majority of cases occur among patients living in sub-Saharan Africa, India, and Southeast Asia [1–6]. The overall burden of cryptococcosis and its influence on morbidity and mortality largely reflects limited access

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to HIV care, antiretroviral drugs, and other anti-infective agents. In more affluent countries, the incidence of cryptococcosis has decreased dramatically among patients with HIV infection [7], and early mortality associated with this disease is generally <10%.

The combination of amphotericin B deoxycholate (AmB) and flucytosine is generally regarded as the gold standard for initial therapy of central nervous system (CNS) cryptococcosis [8]. In vitro and clinical studies suggest that this combination leads to the most-rapid clearance of organisms from cerebrospinal fluid (CSF) [9–11]. AmB is associated with several well-known toxicities, but it is relatively inexpensive and is available in much of the developing world. In contrast, flucytosine is generally available only in more-developed regions, including North America, Western Europe, Japan, and Australia. Extended use of flucytosine often requires monitoring of serum levels to prevent toxicity.

Fluconazole is an azole with significant in vitro activity against most strains of *Cryptococcus neoformans,* and it is recommended as step-down therapy for patients with CNS cryptococcosis who have responded to induction with AmB [8]. Although the drugs are theoretically antagonistic, the combination of AmB and fluconazole has been demonstrated to be effective in vitro and in clinical observations [9, 12–17], although this therapeutic approach has not been studied prospectively on a large scale. Moreover, high-dosage fluconazole (≥12 mg/kg per day) has been reported to be an effective salvage regimen for CNS cryptococcosis [12–14, 17]. Fluconazole is also generally available and inexpensive worldwide, can be orally administered, does not require careful monitoring, and is well tolerated by most patients, even at higher doses. Given these considerations, we conducted a phase II randomized controlled trial that compared the safety and efficacy of AmB alone or in combination with fluconazole at standard (400 mg or 6 mg/kg) or higher (800 mg or 12 mg/kg) daily doses for induction treatment of newly diagnosed cryptococcal meningitis among HIV-infected patients.

METHODS

Study population. Patients who were ≥13 years old and were experiencing a first episode of HIV-associated cryptococcal meningitis were enrolled into this Bacteriology and Mycoses Study Group clinical trial. Exclusion criteria included pregnancy, breast-feeding, concomitant CNS illness that would interfere with assessment of response, creatinine clearance level <50 mL/min, significant liver dysfunction (alanine transaminase level, >5 times the upper limit of normal), coma, anticipated survival <14 days, prestudy antifungal therapy lasting >4 days, and untreated active tuberculosis. Patients receiving primary fluconazole prophylaxis (≤200 mg daily) at enrollment were considered to be eligible for the study. Patients or their authorized representative provided informed consent. The protocol was approved by each site's institutional review board or ethics committee. An independent data safety monitoring board oversaw the study.

Study design. This was a phase II, open label, randomized trial conducted at 8 sites in the United States and 5 sites in Thailand. Patients were randomized into 3 treatment arms via an adaptive randomization system stratifying by country and opening lumbar CSF pressure (≤250 mm vs. >250 mm CSF vs. not done), with the goal of obtaining at least 40 evaluable patients per arm. The 3 treatment arms were as follows: (1) a standard arm that received AmB deoxycholate 0.7 mg/kg/day for 14 days, followed by 400 mg/day fluconazole for 56 days (the AmB arm); (2) low-dose combination therapy with AmB 0.7 mg/kg/day plus fluconazole 400 mg/day for 14 days, followed by fluconazole 400 mg/day for 56 days (the AmB plus Fluc 400 arm); and (3) high-dose combination therapy with AmB 0.7 mg/kg/day plus fluconazole 800 mg/day for 14 days, followed by 800 mg/day fluconazole for 56 days (the AmB plus Fluc 800 arm). AmB could be continued through day 21 at the discretion of the investigator, and all patients were to receive a minimum cumulative dose of AmB 8.4 mg/kg. Fluconazole was administered as a single daily dose; no initial loading dose was administered. Fluconazole doses were adjusted according to weight and decreased renal function; patients weighing <40 kg at baseline received 50% of the randomized dose.

Investigators were encouraged to manage increased intracranial pressure aggressively with additional lumbar punctures or other mechanical interventions; however, the management of an individual patient was left to the discretion of the investigator. CSF samples were obtained for culture at baseline and day 14; for patients with positive culture results on day 14, additional CSF cultures were performed at day 42 and/or day 70. We encouraged investigators to use quantitative methods for all CSF cultures. Cryptococcal meningitis and HIV status were confirmed postrandomization. Randomized patients who were determined to be ineligible on the basis of either negative HIV test results or negative baseline CSF culture results were removed from subsequent treatment allocation calculations.

For patients who received antiretroviral therapy at baseline, antiretroviral therapy was continued throughout the study at the discretion of the investigator. For others, initiation of antiretroviral therapy before study day 42 was strongly discouraged. For all patients who received antiretroviral therapy, we collected clinical and laboratory data concerning the development of immune reconstitution inflammatory syndrome.

Objectives and end points. The primary objectives of this study were to assess safety and tolerability of the treatment

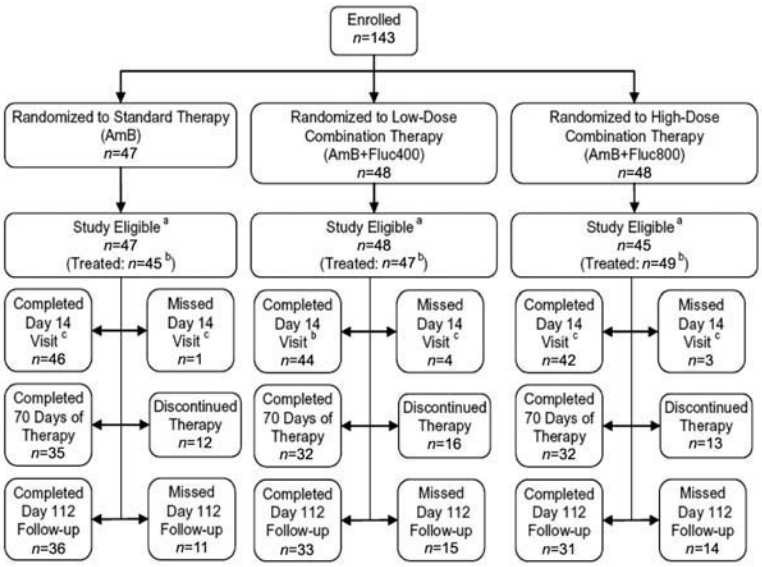

Figure 1. Patient disposition in a phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of human immunodeficiency virus (HIV)–associated cryptococcal meningitis. [a]Includes confirmed HIV-positive and culture-positive for cryptococcal meningitis patients who started therapy. [b]Two patients who were randomized to the standard arm received low-dose combination therapy. Three patients who were randomized to the low-dose combination therapy arm did not have their fluconazole dose adjusted on the basis of baseline weight; these patients were considered to have received high-dose combination therapy. [c]Must have completed assessments required for the primary efficacy end point: death before or culture and neurologic status assessed at day 14 visit.

regimens and to determine whether the safety and efficacy of combination therapy supported development of a phase III trial. Secondary objectives included comparing the treatment arms for efficacy and mortality. The primary safety end point was the number of patients who experienced at least 1 severe, life-threatening, or fatal treatment-related toxicity before day 100. The primary efficacy end point was a composite end point in which success was defined as CSF conversion to negative culture results, stable neurological function, and survival at day 14. A blinded data review committee adjudicated study data pertaining to patient eligibility and both safety and efficacy outcomes.

Analysis populations and methods. All statistical computations were performed using SAS, version 9.1 (SAS Institute). For the primary safety analyses, we included all patients who received study therapy and were also HIV positive and culture-positive for *C. neoformans*. For efficacy analysis, we used the modified intention-to-treat population, which included primary safety analyses patients who received ≤4 days of systemic prestudy antifungal therapy for cryptococcosis, and the per protocol population, which included modified intention-to-treat patients who substantially followed the protocol. Analyses that used the primary safety analyses and modified intention-to-treat populations used randomized treatment arms, whereas analyses that used the per protocol population used actual treatment arms.

For the primary safety end point, the percentage of patients who experienced toxicity and associated 90% confidence intervals (CIs), based on exact binomial methods, were calculated for each treatment arm. Descriptive *P* values were obtained from a 1-sided exact unconditional test for each combination therapy arm that compared the combination therapy arm to the standard arm [18]. In addition, analyses were repeated for the percentage of patients who experienced severe, life-threatening, or fatal toxicities related to fluconazole. Site-reported adverse events were also summarized.

For the primary composite efficacy end point, treatment differences were assessed calculating percentage success at day 14 and associated 90% CIs based on exact binomial methods. In calculating the study sample size, the acceptable difference between success for combination therapy and standard therapy was 10%. Percentages of success and associated CIs were also calculated for days 42 and 70. These analyses were performed on the modified intention-to-treat population, with missing values for the end point considered as treatment failure. Descriptive *P* values were obtained from a 2-sided stratified exact test of the common odds ratio for each combination therapy arm that compared the combination therapy arm with the stan-

Table 1. Baseline characteristics of the modified intention-to-treat population in a phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of human immunodeficiency virus (HIV)–associated cryptococcal meningitis.

Variable	AmB (n = 46)	AmB+Fluc400 (n = 48)	AmB+Fluc800 (n = 41)
Country			
Thailand	32 (69.6)	34 (70.8)	31 (75.6)
United States	14 (30.4)	14 (29.2)	10 (24.4)
Age, mean years ± SD	36.5 ± 8.52	36.4 ± 8.69	35.8 ± 9.36
Sex			
Male	30 (65.2)	31 (64.6)	26 (63.4)
Female	16 (34.8)	17 (35.4)	15 (36.6)
Race			
Asian/Thai	32 (69.6)	34 (70.8)	31 (75.6)
Black	8 (17.4)	10 (20.8)	3 (7.3)
White	4 (8.7)	4 (8.3)	6 (14.6)
Other	2 (4.4)	0	1 (2.4)
$CD4^+$ T cell count, median cells/mm^3 (range)	18 (1–123)	17 (0–80)	15 (0–94)
Viral load, median copies/mL (range)	272,000 (400–1,342,580)	369,000 (50–1,000,000)	169,000 (216–1,000,000)
Opening pressure			
>250 mm CSF	22 (47.8)	26 (54.2)	22 (53.7)
⩽250 mm CSF	20 (43.5)	19 (39.6)	17 (41.5)
Not done	4 (8.7)	3 (6.3)	2 (4.9)
CSF cryptococcal antigen titer, median (range)	2048 (4–32768)	1024 (4–71024)	1024 (4–16384)
MMSE, mean score ± SD	25.5 ± 5.21	25.3 ± 5.07	23.4 ± 7.25
Received prestudy fluconazole and/or flucytosine[a]			
Yes	6 (13.0)	4 (8.3)	2 (4.9)
No	40 (87.0)	44 (91.7)	39 (95.1)
Receipt of antiretroviral therapy			
Yes	5 (10.9)	3 (6.2)	3 (7.3)
No	41 (89.1)	45 (93.8)	38 (92.7)

NOTE. Data are no. (%) of patients, unless otherwise indicated. AmB, amphotericin B deoxycholate; AmB+Fluc400, amphotericin B deoxycholate plus fluconazole administered at a dosage of 400 mg; AmB+Fluc800, amphotericin B deoxycholate plus fluconazole administered at a dosage of 800 mg; CSF, cerebrospinal fluid; MMSE, Mini-Mental Status Examination; SD, standard deviation.

[a] Of the patients who received prestudy fluconazole and/or flucytosine; only 2 patients received >3 days of fluconazole (1 in the AmB arm and 1 in the AmB+Fluc400 arm).

dard arm. Time to death was assessed descriptively using Kaplan-Meier analysis with right censoring.

RESULTS

Patient disposition. A total of 143 HIV-positive patients were enrolled into the study (100 in Thailand and 43 in the United States) from May 2005 through August 2007 (figure 1). One patient had a sterile baseline CSF culture and was determined to be ineligible for the study. Two other patients were removed from study before receiving therapy because of withdrawal of consent (1 patient) and poor renal function (1 patient). These patients were excluded from the primary safety analyses population. Five additional patients were excluded from the modified intention-to-treat population on the basis of having experienced a previous episode of cryptococcosis (1 patient) and having received substantial prestudy antifungal therapy or rifampicin (4 patients). Baseline demographic, HIV, and cryptococcal meningitis disease severity characteristics of the modified intention-to-treat population were similar among treatment arms (table 1).

Treatment course. The first 14 days of study therapy were administered while patients were hospitalized. Remaining doses of fluconazole were dispensed and treatment compliance was measured using pill counts at study visits. Overall compliance was comparable between treatment arms. The mean (± standard deviation [SD]) duration of fluconazole study therapy for the AmB arm, the AmB plus Fluc 400 arm, and the AmB plus Fluc 800 arm were 51.1 ± 15.8, 54.1 ± 24.2, and 58.0 ± 20.3 days, respectively. The median duration of all therapy was 57 days in the AmB arm and 70 days in the combination therapy

Table 2. Primary safety assessment of the number of patients with severe, life-threatening, or fatal treatment-related toxicities.

Variable	AmB (n = 47)	AmB+Fluc400 (n = 48)	AmB+Fluc800 (n = 45)
Related to either study drug			
Overall			
Patients with event	19 (40.4)	18 (37.5)	14 (31.1)
90% CI, %[a]	28.3–53.5	25.8–50.4	19.9–44.3
P[b]		.573	.794
By severity[c]			
Severe	13 (27.6)	13 (27.1)	9 (20.0)
Life-threatening	6 (12.8)	5 (10.4)	5 (11.1)
Fatal	0	0	0
By relatedness[c]			
Probably related	16 (34.0)	16 (33.3)	12 (26.7)
Definitely related	3 (6.4)	2 (4.2)	2 (4.4)
Related to fluconazole			
Overall			
Patients with event	0	0	2 (4.4)
90% CI, %[a]	0.0–6.2	0.0–6.1	0.8–13.3
P[b]		>.99	.098
By severity[c]			
Severe	0	0	1 (2.2)
Life-threatening	0	0	1 (2.2)
Fatal	0	0	0
By relatedness[c]			
Probably	0	0	2 (4.4)
Definitely	0	0	0

NOTE. Data are no. (%) of patients, unless otherwise indicated. AmB, amphotericin B deoxycholate; AmB+Fluc400, amphotericin B deoxycholate plus fluconazole administered at a dosage of 400 mg; AmB+Fluc800, amphotericin B deoxycholate plus fluconazole administered at a dosage of 800 mg; CI, confidence interval.

[a] CI based on exact binomial methods.

[b] Descriptive P value based on a 1-sided exact unconditional test for each combination therapy arm that compared the combination therapy arm with the standard arm using procedures described in Suissa and Schuster [18].

[c] If a patient experienced >1 event, the patient is counted only once for the most-severe or most-related event.

arms. Overall, 39 patients discontinued study therapy before day 70. The primary reasons were death (19 patients), adverse events (3 patients), and loss to follow-up (7 patients).

Safety and tolerability. More than 30% of patients in each arm experienced severe toxicities related to AmB or fluconazole (table 2). These events included (in descending order of frequency) hypomagnesemia, hypokalemia, anemia, AmB infusion intolerance, decreased renal function, psychosis, and subdural hematoma. Neither of the combination therapy arms experienced a higher incidence of toxicities than the standard therapy arm. Most toxicities were related to AmB. Overall, only 2 patients experienced a severe or life-threatening fluconazole-related toxicity (both patients were in the AmB plus Fluc 800 arm). One patient experienced psychosis after receiving 1600 mg of fluconazole in a single day, and 1 patient experienced a subdural hematoma while receiving fluconazole and warfarin concomitantly. Results were consistent among countries and baseline opening pressure categories. Fluconazole dosage adjustment relating to changing renal function was common and occurred in 10 (22%), 17 (36%), and 27 (55%) of the patients in the AmB arm, the AmB plus Fluc 400 arm, and the AmB plus Fluc 800 arm, respectively. Except for nausea, the percentage of patients who experienced site-reported adverse events in the combination therapy arm was comparable to or less than the percentage in the standard arm who experienced site-reported adverse events. A greater percentage of patients experienced nausea in the combination therapy group than in the standard therapy group ($P = .19$, for comparison of all treatment arms). Also, a greater percentage of patients in the AmB plus Fluc 800 arm than in the standard arm reported

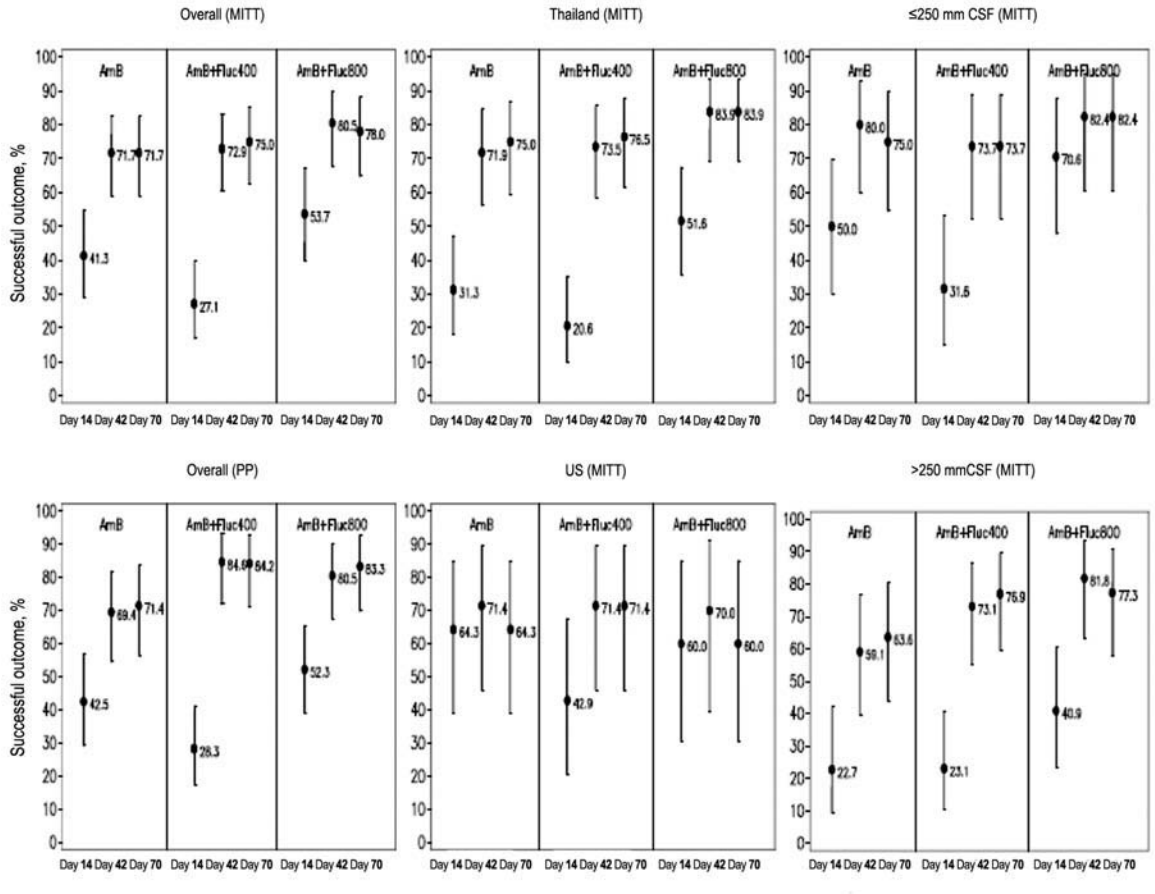

Figure 2. Percentage success by treatment and visit for primary composite outcome. Success is defined as having qualitative fungal culture results negative for cryptococcal meningitis, being neurologically stable or improved, and being alive. The dots represent the estimates of the percentage of patients who experienced success and the lines represent the corresponding 90% exact binomial confidence intervals. For baseline opening pressure category, "not done" is not included, because only 9 patients had missing baseline opening pressure results. MITT, modified intention-to-treat population; PP, per protocol population.

possible, probable, or definite treatment-associated adverse events that were dose limiting (14.3% vs. 8.9%) or serious (12.2% vs. 6.7%). The most frequent dose-limiting adverse events were related to decreased renal function. On average, all treatment arms experienced a decrease from baseline creatinine clearance level for days 7, 14, and 42. Higher mortality was observed in the standard therapy arm than in the combination therapy arms (22.2%, 17%, and 18.4% for the AmB arm, the AmB plus Fluc 400 arm, and the AmB plus Fluc 800 arm, respectively).

Efficacy. At day 14, a greater percentage of patients in the modified intention-to-treat population had experienced success, as defined by the composite end point, in the AmB plus Fluc 800 arm than in the AmB arm; however, a smaller percentage of patients experienced success in the AmB plus Fluc 400 arm than in the AmB arm (figure 2). A higher percentage of US patients than Thai patients experienced success in each arm, and the differences in outcome between arms were smaller, compared with the differences between arms for Thai patients. At days 42 and 70, the percentage of patients with success was high in all arms (>70%), but the highest percentage of success was observed among patients in the combination therapy arms. Few patients had experienced neurological deterioration at day 14; thus, the primary composite end point was largely determined by mortality and culture status.

Of 26 deaths occurring in the modified intention-to-treat population, 10 occurred in patients with opening pressure ≤250 mm CSF (15%, 21%, and 18% for the AmB arm, the AmB plus Fluc 400 arm, and the AmB plus Fluc 800 arm, respectively), and 16 occurred in patients with opening pressure >250 mm CSF (32%, 19%, and 18% for the AmB arm, the AmB plus Fluc 400 arm, and the AmB plus Fluc 800 arm, respectively). There was a trend toward improved early survival among patients in the AmB plus Fluc 800 arm, compared with

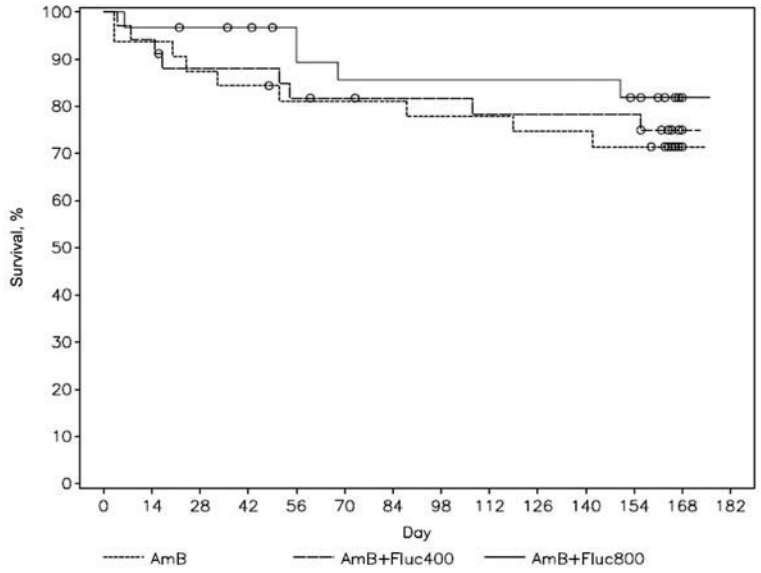

Figure 3. Kaplan Meier estimates of overall survival for the modified intention-to-treat population. Circles denote censored observations. AmB, amphotericin B deoxycholate; AmB+Fluc400, amphotericin B deoxycholate plus fluconazole administered at a dosage of 400 mg; AmB+Fluc800, amphotericin B deoxycholate plus fluconazole administered at a dosage of 800 mg.

the AmB arm (figure 3). The most common primary causes of death were sepsis, cryptococcal meningitis, and other opportunistic infections.

Use of antiretroviral therapy did not differ between treatment arms at baseline (8.7%, 4.2%, and 7.3% for the AmB arm, the AmB plus Fluc 400 arm, and the AmB plus Fluc 800 arm, respectively). At study day 42, these values were 17.4%, 4.2%, and 22.0%, respectively ($P < .05$). Among all patients who received antiretroviral therapy, immune reconstitution inflammatory syndrome was observed in 8.3%, 10.3%, and 21.9% of patients in the AmB arm, the AmB plus Fluc 400 arm, and the AmB plus Fluc 800 arm, respectively ($P = .22$).

DISCUSSION

There is a critical global need to develop new approaches to antifungal therapy of HIV-associated CNS cryptococcosis. The 2 compounds that were examined in this clinical trial, AmB and fluconazole, are not ideal agents for the treatment of cryptococcosis; however, both are generally available and reasonably affordable in many parts of the world. The major objective of this study was to determine whether trends in safety and efficacy with combination therapy could justify pursuing a phase III trial powered to determine whether combination therapy offers a significant advantage over therapy with AmB alone. The results are encouraging and suggest a possible role for the combination of AmB and high-dose fluconazole (800 mg/day or 12 mg/kg/day) as initial therapy for HIV-associated cryptococcosis.

Clinical observations among patients with HIV-associated cryptococcosis suggest that CSF culture positivity after 2 weeks of antifungal therapy predicts poor outcomes [19] and that early CSF sterilization should be an important goal of therapy. The landmark study by Brouwer et al. [9], which involved patients with HIV-associated cryptococcosis, demonstrated that AmB plus flucytosine was the most rapidly fungicidal combination in CSF, compared with other AmB-containing regimens, including AmB plus fluconazole, AmB plus fluconazole and flucytosine, and AmB alone. Subsequently, Bicanic et al. [10] demonstrated that AmB administered at a dosage of 1.0 mg/kg/day plus flucytosine was more rapidly fungicidal in CSF than was AmB administered at a dosage of 0.7 mg/kg/day plus flucytosine. These studies provide important insights into initial therapy for CNS cryptococcosis, but no study of combination therapy has demonstrated a significant reduction in mortality.

Clinical experience with fluconazole administered alone or in combination with AmB for the treatment of CNS cryptococcosis has generally been favorable [12–14, 17]. In addition, animal studies suggest that the combination of AmB plus fluconazole is more fungicidal and is associated with better survival than is therapy with AmB alone [15, 16]. Moreover, the study by Brouwer et al. [9] demonstrated a trend toward more-rapid CSF sterilization with AmB plus fluconazole than with AmB alone. Taken together, these observations and the general availability of fluconazole and AmB led us to design the current prospective phase II study.

Several important observations from this trial point to potential benefits of combination therapy. First, the combination of AmB and fluconazole at either 400 or 800 mg daily, ad-

ministered for 14 days and followed by the randomized dosage of fluconazole alone for 56 days, is well tolerated and safe, compared with AmB alone followed by fluconazole. No significant differences in toxicities or adverse events that led to therapy discontinuation were found among the 3 arms. Most toxicity was predictable and associated with AmB. Fluconazole-related toxicity was uncommon, including in the high-dosage arm. This is similar to observations from a large study that compared AmB plus high-dosage fluconazole to high-dosage fluconazole alone for the treatment of candidemia [20]. Finally, the combination of AmB plus fluconazole 800 mg/day led to numerically better outcomes at each interval assessment, compared with AmB followed by fluconazole.

The poorest outcomes at 14 days were observed among patients in the lower-dosage fluconazole combination therapy arm. This difference was not evident at 42 and 70 days of follow-up, more closely approximating the results seen in the higher-dosage fluconazole combination therapy arm. These results at day 14 in the lower-dosage combination therapy arm are not easily explained. A careful review of the clinical and baseline laboratory data did not reveal any significant differences in terms of demographic characteristics, HIV load, $CD4^+$ cell count, baseline level of cryptococcal antigenemia, positive blood culture results, CSF opening pressure, or any other clinical or mycologic parameter that might have adversely affected outcome disproportionately. Fewer patients in this arm, compared with the other 2 arms, received antiretroviral therapy at 6 weeks, but this did not impact the primary end point of success at 2 weeks. It is possible that the addition of lower-dosage fluconazole to AmB results in antifungal antagonism, which caused the slower rate of clearance in the CSF, compared with the CSF clearance rates in the other 2 arms. The antagonistic interaction between AmB and fluconazole against an isolate of *C. neoformans* has been reported in vitro; however, this antagonism occurred when the organism was exposed to fluconazole before it was exposed to AmB [21]. In the current study, the AmB was administered before fluconazole was administered.

Our study had several limitations. This phase II study was not powered to demonstrate statistically significant differences in efficacy between treatment arms. Nonetheless, we predetermined that a $\geqslant$10% favorable difference in outcome for either of the combination therapy arms, compared with conventional therapy with AmB, would be sufficient to develop an adequately powered phase III comparative study. These differences in efficacy were most evident among Thai patients and were much less dramatic among US patients. Although there are several possible explanations for this disparity, there are few explanations supported by the study data. On the basis of a small sample size, we could discern few differences in baseline characteristics, clinical management, and study medication compliance. There were no differences in prestudy antiretroviral therapy or fluconazole exposure. The study was open-label, but we believe that this was an appropriate design for a phase II nonpivotal study. Finally, we were unable to obtain quantitative CSF cultures from all sites, thus limiting our ability to make conclusions about the comparative antifungal activity of the three regimens and to correlate these results with clinical outcome

The results of this study raise an important therapeutic question: given the safety and tolerability of combination therapy with AmB and high-dose fluconazole seen in this and other trials, is the difference in efficacy, compared with that of AmB alone, sufficient to justify moving toward a larger, adequately powered, phase III, double-blinded study? On the basis of these safety and efficacy data, the universal availability of oral fluconazole, and the relative availability and affordability of intravenous AmB, we believe that there is a strong rationale to support moving forward with the development of a definitive trial. The potential impact on the treatment of cryptococcosis could be substantial, not only in the developing world, but in other areas of the world where flucytosine is available but where serum levels cannot be easily monitored and in situations where flucytosine is otherwise contraindicated. The above concerns notwithstanding, these are promising preliminary data and have the potential to significantly influence early therapy for HIV-associated cryptococcal meningitis.

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