Comparison of One Week with Two Week Regimens of Amphotericin B Both followed by Fluconazole in the Treatment of Cryptococcal Meningitis among AIDS Patients

Somsit Tansuphaswadikul MD*, Wirach Maek-a-Nantawat MD**,
Benjaluck Phonrat MSc**, Lamom Boonpok BN*,
Aneley Getahun MCTM**, Punnee Pitisuttithum MD**

** Bamrasnaradura Infectious Disease Institute, Department of Disease Control, Nonthaburi*
*** Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University*

Background: *Amphotericin B treatment in cryptococcosis requires daily hospital visits or admission. Its toxicities and hospital costs have been concerned. Short course amphotericin B regimen warrants to be evaluated.*
Objective: *To compare the safety and efficacy of one-week (AmB1) with two-week (AmB2) amphotericin B both followed by fluconazole.*
Material and Method: *57 AIDS with cryptococcal meningitis were randomly assigned to either AmB1 or AmB2. Microbiological and clinical clearances were the outcomes of the study.*
Results: *The treatment success at 6 weeks was 63.3% in AmB1 and 70.4% in AmB2 (p = 0.574). Clinical assessment at week 10 and renal toxicities were not significantly different between both regimens. Mortality rate was 14% however, 75% of deaths were in AmB2.*
Conclusion: *AmB1 was comparably effective and safe as the standard AmB2 regimen in the treatment of AIDS related cryptococcal meningitis. It can be an alternative regimen to lower hospital based care and improve cost effective for source limiting health care centers.*

Keywords: *Cryptococcal meningitis, AIDS, Amphotericin B, Thailand*

J Med Assoc Thai 2006; 89 (10): 1677-85
Full text. e-Journal: *http://www.medassocthai.org/journal*

Central nervous system (CNS) infections caused by *Cryptococcus neoformans* predominantly presenting as meningitis, have been a major opportunistic fungal infection among the enlarging immunocompromized patients through the HIV epidemic around the world[1,2]. Among AIDS patients in Thailand, cryptococcosis is the second most common opportunistic infection after tuberculosis. However, it becomes the number one among opportunistic infections of central nervous system in advanced HIV disease[3]. Amphotericin B deoxycholate (0.7-1 mg/kg daily) with or without 5- flucytosine (100 mg/kg daily) intravenously for two weeks, followed by eight weeks of fluconazole (400 mg daily) is the recommended first line treatment for AIDS associated cryptococcal meningitis[4,5]. Intravenous amphotericin B is associated with severe toxicities, such as nephrotoxicity, electrolyte imbalance, and bone marrow suppression[6,7]. In Thailand, with unavailability of flucytosine, amphotericin B alone is routinely administered at the same doses, which is an acceptable alternative[5,8]. Moreover, patients treated with this regimen require admission or need to come to the hospital everyday for intravenous infusion and need monitoring to be aware of prolonged use toxicity of amphotericin B. Therefore, the present study aimed to compare

Correspondence to : Pitisuttithum P, Clinical Infectious Diseases Research Unit, Department of Clinical Tropical Medicine Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Rd, Bangkok 10400, Thailand. Phone: 0-2643-5599, Fax: 0-2643-5598

the safety and efficacy of short course (one-week) amphotericin B with the standard regimen of two-week amphotericin B both followed by fluconazole. If a one-week amphotericin B is comparably effective and safe as the standard two-week induction treatment then, it will significantly reduce the cost of treatment and hospital stays in resource limited settings.

Material and Method

This prospective, randomized, and open-label clinical trial was conducted at the Bamrasnaradura Infectious Disease Institute, Department of Disease Control, Nonthaburi, Thailand. The inclusion criteria included: age > 13 years, documented seropositive anti-HIV antibody by ELISA test and confirmed by another, different test; first episode of cryptococcal meningitis diagnosed by Indian ink staining of cerebrospinal fluid (CSF) specimen (confirmed by CSF culture), Karnofsky score of $\geq$ 70, and no significant impairment of hepatic or renal functions (alanine aminotransferase/aspartate aminotransferase $\leq$ 5 times the upper limit of normal or serum creatinine $\leq$ 2.0 mg/dl and blood urea nitrogen (BUN) $\leq$ 40 mg/dl). Patients with a history of recurrent or relapse of cryptococcal meningitis, concurrent or previous treatment with systemic antifungal agents within 4 weeks, other known CNS infections, Glasgow Coma Scale $\leq$ 8, known hypersensitivity to amphotericin B and/or fluconazole, and pregnancy/lactation were excluded. From November 2002 to September 2003, 57 patients attending the out-patient, in-patient, and ambulatory care units of the Institute for the treatment of meningitis were enrolled as per criteria. Study subjects were randomly allocated to either AmB1, which received one week of amphotericin B (0.7 mg/kg/day) or AmB 2, who received two weeks of amphotericin B (0.7 mg/kg/day). Subsequently, all patients received fluconazole 400 mg/day until at least one CSF culture showed negative or until completion of the 8 week standard treatment. Afterward, fluconazole 200 mg daily was then prescribed as secondary prophylaxis. The randomization was performed by a method of using the random number table list. All patients gave their informed consent prior to enrollment to the study. The present study was approved by the Institutional Review Board of Bamrasnaradura Infectious Disease Institute.

Clinical and laboratory evaluations of the study subjects were done at baseline and follow up visits at week 1, week 2, week 4 and week 6 and week 10. Lumbar puncture (LP) for CSF analysis, Indian ink and culture for *Cryptococcus neoformans* were performed at the end of week 2, 4, and 6. Patients with high CSF opening pressure were treated by repeated pressure releasing LP when there was worsening neurological signs and symptoms. The main treatment outcome was considered successful in terms of mycological parameter if at least one CSF culture performed at 2 weeks interval was negative prior to the end of 6 week follow-up. The clinical response in terms of clinical resolution after 8 week's duration of treatment was considered successful as the secondary outcome. Clinical signs/symptoms including fever, headache, nausea, vomiting, mental status, body weight, and CSF opening pressure (OP) were assessed at each follow up visit. Complete blood count, liver and renal function tests were assessed at the end of amphotericin B treatment, i.e. at week 1 in AmB1 group and at week 2 in AmB2 group. All patients were hospitalized for the duration of amphotericin infusion (one week for AmB1 and two weeks for AmB2) then, outpatient follow-up at the ambulatory care unit continued as scheduled.

The data was collected and completed in the case record forms, and then entered in the computer and analyzed by Microsoft Excel program and SPSS Version 11.5 software. Outcome of the analysis was performed as intention-to-treat analysis. The categorical data were reported in percentages or proportions and the comparison was performed between the groups by Chi-square test or Fisher exact tests. The numerical data were presented as median with Inter-quartile range (IQR) and comparison between groups was performed by Mann-Whitney U test. Wilcoxon signed rank test was used to compare clinical outcomes and adverse events between prior and after each treatment group. Survival analysis using Kaplan Meier method was performed to estimate median time to clearance of CSF culture and cumulative adherence to treatment. A p-value of less than 0.05 was considered significant.

Results

Thirty and twenty-seven eligible study subjects were randomly assigned to AmB1 and AmB 2 treatment, respectively. Baseline demographic data is shown in Table 1. Age, gender and body weight were comparable between the two groups. Overall, the median age (IQR) of the population was 35 years (30-42.5 years) and the majority of the subjects were male (63.2%). Half of the patients were married (50.9%). The median weight (IQR) at baseline was 46.8 kg (43.0-52.8 kg). Twenty patients (35.1%) (20/57) had concurrent treatment for tuberculosis (33.3% vs 37% were in AmB1 and AmB2, respectively, p = 0.77). One patient in AmB1 had CMV retinitis. Ninety-five percent of all patients

Table 1. Baseline demographic, clinical and laboratory characteristics of patients in AmB1 and AmB2 arms

	AmB1 n = 30	AmB2 n = 27	p-value
Demography			
Median age in years (IQR)	36 (30.75-43.25)	34 (29.00-41.00)	0.298*
Sex:Male	19 (63.3%)	17 (63.0%)	0.977**
Marital status: Single	9 (30.0%)	8 (29.6%)	
Married	15 (50.0%)	14 (51.9%)	0.936**
Clinical parameters			
Median weight in Kg (IQR)	45.2 (41.9-51.1)	49.3 (45.5-55.0)	0.016*
Headache	29 (96.7%)	25 (92.6%)	0.492**
Fever	12 (40.0%)	15 (55.6%)	0.240**
Nausea/Vomiting	22 (73.3%)	23 (85.2%)	0.273**
Weight loss	17 (56.7%)	16 (59.3%)	0.843**
Cough	11 (36.7%)	9 (33.3%)	0.792**
Blur vision	4 (13.3%)	6 (22.2%)	0.378**
Hearing defect	2 (6.7%)	1 (3.7%)	0.617**
Seizure	2 (6.67%)	3 (11.1%)	0.554**
Median temperature (IQR)	38°C (37-39)	38°C (37-39)	
Neck rigidity	16 (53.3%)	12 (44.4%)	0.50**
Lymphadenopathy	4 (13.3%)	7 (25.9%)	0.229**
Hepatomegaly	3 (10%)	6 (22.2%)	0.206**
Splenomegaly	1 (3.3%)	3 (11.1%)	0.251*
Investigations	n = 30	n = 27	
CSF OP (cm of H_2O)	32.5 (22-40.5)	31.0 (23-46)	0.879*
Hematology	n = 28	n = 27	
Hemoglobin (g/dl)	10.9 (9.0-11.8)	10.8 (9.5-12.5)	0.743*
WBC (x 10^3/ml)	3.79 (2.87-5.31)	4.82 (3.60-4.80)	0.023*
Platelet (x 10^3/ml)	232 (172-305)	205 (144-308)	0.762*
Renal function			
BUN (mg/dl)	n = 29	n = 27	
	13.4 (9.8-19.2)	13.0 (9.0-17.0)	0.629*
Creatinine (mg/dl)	n = 28	n = 27	
	0.75 (0.60-0.91)	0.85 (0.63-1.04)	0.248*
CSF analysis			
WBC (cell/mm^3)	n = 28	n = 26	
	8.0 (2.2-33.2)	11.5 (3.5-25.5)	0.621*
Glucose (mg/dl)	n = 30	n = 26	
	39.5 (33-47.5)	43.5 (30.7-50.7)	0.693*
Protein (mg/dl)	n = 30	n = 26	
	54.8 (29.0-75.2)	57.2 (38.5-79.5)	0.397*

* p-value by Mann-Whitney U test, ** p-value by Chi square test
CSF: cerebrospinal fluid OP: open pressure BUN: blood urea nitrogen WBC: white blood cells
IQR = Inter quartile range

(54/57) presented with headache, 79% (45/57) with nausea and vomiting, 57.9% (33/57) with weight loss, 47.0% (27/57) with fever, 35.1% (20/57) with a cough. Only 17.5% (10/57) and 8.8% (5/57) complained of blur vision and had a history of seizure prior to admission. Median duration (IQR) of complaint was 2 weeks (1-3). Median time (IQR) of known HIV infection before developing cryptococcosis was 10 weeks (0-110). All clinical parameters were also comparable between both treatments. The baseline median (IQR) cerebrospinal fluid open pressure (CSF OP) was 32 cm H_2O (23-43), 80.0% of which were more than 20 cm H_2O. There was no statistical difference of CSF OP between both groups of treatment.

Mycological outcome

Treatment success at week 6, defined at least one CSF culture negative at 2 week intervals, was 63.3% (19/30) in the AmB1 group and 70.4% (19/27) in the AmB2 group (p = 0.574). However, most of the patients showed two consecutive CSF cultures negative. Only six in AmB1 (20.0%) and four in AmB2 (14.8%) had only one CSF culture negative (p = 0.734) (Table 2). The cumulative CSF culture clearance was 24.6% at week 2 (26.7% in AmB1 and 22.2% in AmB2, p = 0.935 by Chi square test), 59.6% at week 4 (60.0% in AmB1 and 59.3% in AmB2, p = 0.646), and 66.7% at week 6 (63.3% in AmB1 and 70.4% in AmB2 p = 0.778) (Fig. 1). Estimated median time to CSF clearance was 28 days for both groups.

Clinical outcome

At week 6 of treatment, there was a significant drop in CSF OP from the baseline, p = 0.005 by Wilcoxon signed ranks test (p = 0.109 in AmB1 and 0.022 in AmB2). There was no significant increase in body weight from the baseline at week 6 of treatment; p = 0.059 in AmB1 and 0.889 in AmB2 by Wilcoxon signed ranks test respectively. At week 10, there were overall significantly improved clinical responses in headache (p < 0.0001 in AmB1, p < 0.0001 in AmB2), nausea and vomiting (p = 0.001 in AmB1, p < 0.0001 in AmB2), and fever (p = 0.008 in AmB1, p = 0.001 in AmB2). However, there was no significant difference of each clinical parameter between groups. Twenty patients (35.1%) started antiretroviral therapy (ART) during the 10 weeks' follow up period. The median time for initiation of ART was 4 weeks. Highly active antiretroviral therapy (HAART) regimen treated in all cases was combined with stavudine (d4T)/lamivudine (3TC)/ Nevirapine (NVP) made by Thai Government Pharmaceutical Organization (GPOvir®). Three patients in each group, receiving HAART developed cryptococcosis. No one in the treatment success group experienced worsening cryptococcosis within 4-6 weeks after HAART initiation.

Mortality

The overall mortality rate was 14% (8/57) at week 10, with six deaths in AmB2 and two deaths in AmB1. The AmB2 had a higher mortality rate than AmB1 but was not statistically significant (22.2% vs 6.7%, p = 0.132 by Fisher's exact test). Among the deaths, median time to death was 9.5 days (5-36 days) after initiation of treatment. All except one death (co-infection with pulmonary tuberculosis plus sepsis) were attributed to cryptococcal meningitis. At week 10 twenty-nine patients (50.9%) had complete follow up and the mean survival time was 44 days (95%CI 37-51 days), 40 days (95%CI 30-50) in AmB1 and 49 days (95%CI 39-59) in AmB2. The cumulative survival of the study is shown in Fig. 2. Twenty patients (35.1%) were lost to follow-up, out of which 65% occurred within the first two weeks of treatment.

Adverse events

Patients were followed up for adverse events at day1, week1, week2, week4, and week6. There were no severe or life threatening adverse events of amphotericin B during the present study. All treatments were well tolerated and no drug treatment had to be withdrawn within the first two weeks because of side effects. The median baseline creatinine was 0.75mg/dl (0.60-0.91) in AmB1 and 0.85 (0.63-1.04) in AmB2, p = 0.248 by Mann-Whitney test (Table 1). Amphotericin related nephrotoxicity defined as serum creatinine > 2.0 mg/dl (normal value 0.5-1.2 mg/dl) occurred 19.5% of patients (18.5% in AmB1 and 21% in AmB2, p = 0.832) and 10% of patients (0% in AmB1 and 14.3% of

Table 2. Outcomes at 10 week follow up regarding treatment regimen

Outcome	AmB1 n = 30	AmB2 n = 27	Total	p-value*
Treatment success*	19 (63.3%)	19 (70.4%)	38 (66.7%)	0.574
No treatment success				
Death	2 (6.7%)	6 (22.2%)	8 (14.0%)	0.09
CSF culture positive	2 (6.7%)	5 (18.5%)		
Lost follow up	15 (50.0%)	4 (14.8%)	19 (33.3%)	0.005
CSF culture positive	9 (30.0%)	3 (11.1%)		

* p-value by Chi square test CSF: cerebrospinal fluid
AmB1: 1 week regimen of amphotericin B AmB2: 2 week regimen of amphotericin B

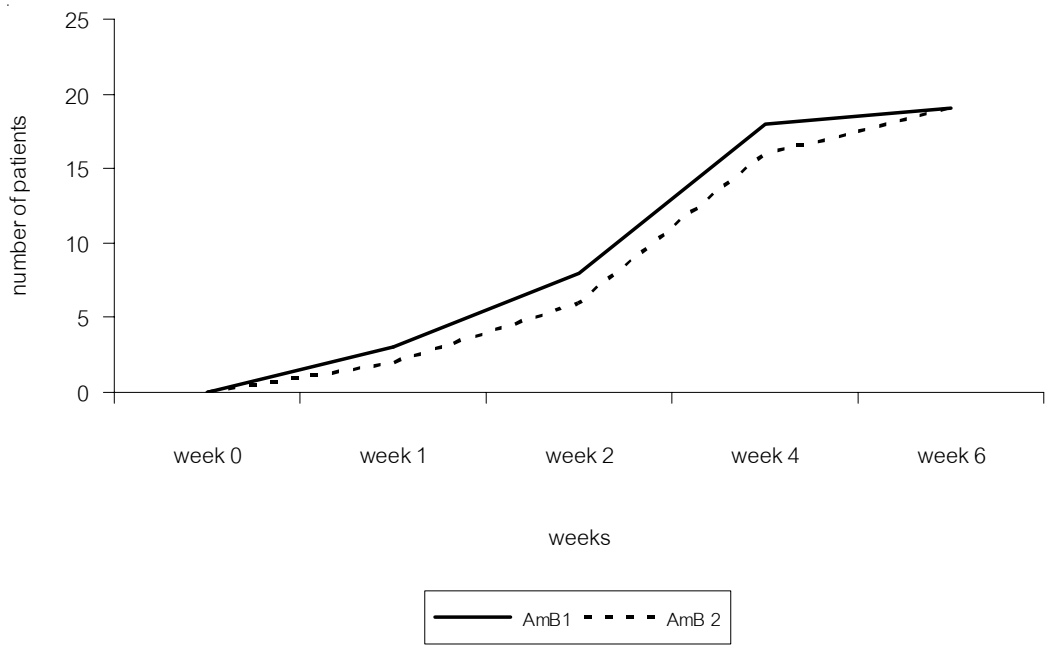

Fig. 1 Cumulative culture clearance in AmB1 and AmB2 arms

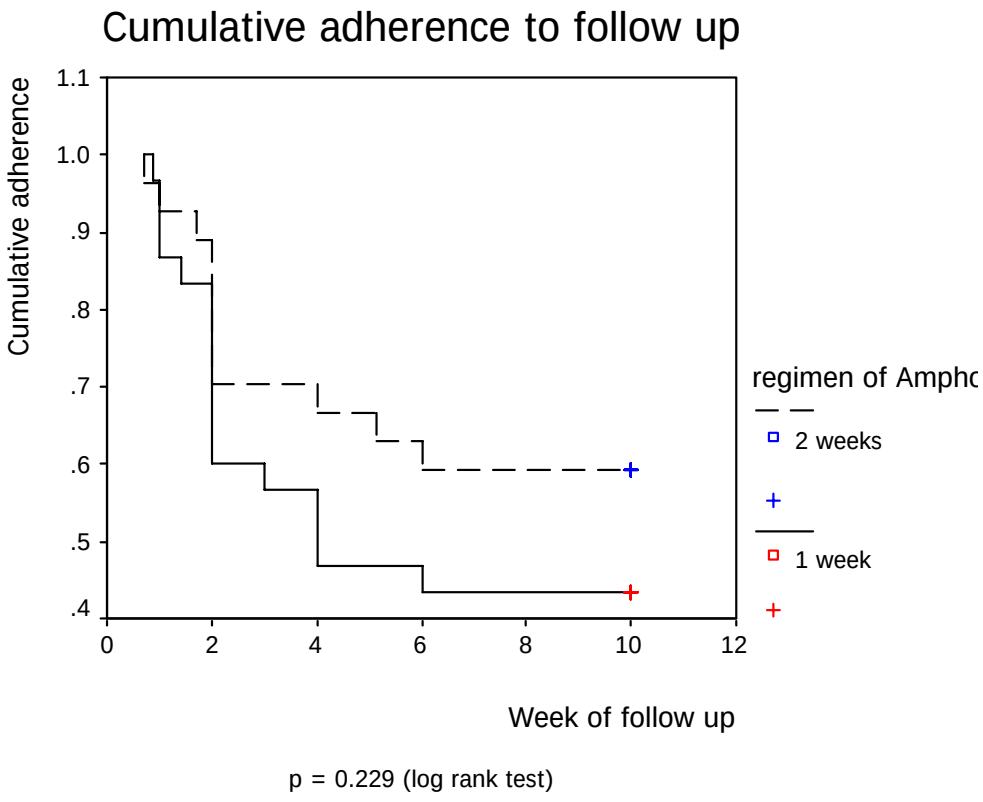

Fig. 2 Cumulative adherence to the AmB1 and AmB2 arm treatments

AmB2, p = 0.534) at week 1 and week 2, respectively. 43.5% of patients (39.3% in AmB1 and 50% in AmB2, p = 0.479) and 31% of patients (22.2% in AmB1 and 35% of AmB2, p = 0.498) had hypokalemia (K ≤ 3.0 meq/L) at week 1 and week 2. At the end of amphotericin therapy, there was no statistically significant difference between the two treatments in terms of increase in serum creatinine (p = 0.349) or increase in serum BUN (p = 0.790), decrease in hemoglobin (p = 0.102) or decrease in platelet level (p = 0.242) (Table 3). About serum potassium levels during therapy, there was no significant change between both groups at week 1 (p = 0.687) and week 2 (p = 0.39). Changes in hematological indices and renal functions in the two treatment groups after administration of amphotericin B were analyzed and appeared in only the patients who had results of investigations at both time points of analysis (Table 4).

Discussion

The standard treatment for AIDS related cryptococcal meningitis is amphotericin B with or without flucytosine for two weeks followed by fluconazole for 8 weeks however, the optimal dosage and optimal duration of amphotericin B in AIDS related infection remains uncertain[9]. To the authors' knowledge, no clinical trial comparing one week amphotericin with two weeks has previously been reported. Moreover, a study by Pitisuttithum et al demonstrated an exponential decrease in CSF cryptococcal count in the first one week of amphotericin B administration[10]. Therefore, the authors aimed to assess whether treatment with one week amphotericin B was at least as effective and safe as the standard two weeks treatment. If the efficacy and safety between the two treatment regimens were equivalent or comparable, then this would alleviate

Table 3. Comparison of hematological indices and renal function for AmB1 and AmB2 arm at baseline and week 2

	Baseline			Week 2		
	AmB1	AmB2	p-value*	AmB1	AmB2	p-value*
Creatinine (mg/dl)	n = 28	n = 27		n = 9	n = 21	
	0.75 (0.60-0.91)	0.85 (0.63-1.04)	0.248	0.92 (0.74-1.11)	1.07 (0.77-1.51)	0.349
BUN (mg/dl)	n = 29	n = 27		n = 9	n = 21	
	13.4 (9.8-19.2)	13.0 (9.0-17.0)	0.629	19.0 (9.6-30.8)	14.0 (10.5-27.0)	0.790
Hb (g/dl)	n = 28	n = 27		n = 20	n = 22	
	10.9 (9.0-11.8)	10.8 (9.5-12.5)	0.743	9.0 (7.1-10.2)	7.9 (6.9-8.8)	0.102
Platelet (x 10^3/ml)	n = 28	n = 27		n = 20	n = 22	
	232 (172-305)	205 (144-308)	0.762	208 (135-381)	170 (116-291)	0.242

* p-value by Mann-Whitney U test , median (IQR)

Table 4. Comparison of hematological indices and renal function at baseline and week 1 for AmB 1 arm, baseline and week 2 for AmB 2 arm

	AmB1			AmB2		
	Baseline	Week1	p-value*	Baseline	Week2	p-value*
Hb (g/dl)	n = 26	n = 26		n = 21	n = 21	
	10.8 (7.2-14.2)	9.2 (5.4-12.1)	<0.001	11.2 (8.6-15.2)	7.9 (5.1-10.4)	<0.001
WBC (x 10^3/ml)	n = 26	n = 26		n = 21	n = 21	
	3.6 (1.8-7.6)	3.7 (1.5-14.6)	0.121	4.8 (1.4-8.9)	3.5 (1.6-7.4)	<0.001
Platelet (x 10^3/ml)	n = 26	n = 26		n = 22	n = 22	
	232 (40-511)	181 (40-418)	0.002	222 (73-489)	170 (59-535)	0.002
BUN (mg/dl)	n = 26	n = 26		n = 21	n = 21	
	13.6 (6.4-33.1)	17 (7-81)	0.012	13.0 (4-32)	14 (4-44)	0.076
Creatinine (mg/dl)	n = 25	n = 25		n = 21	n = 21	
	0.74 (0.50-1.59)	1.16 (0.70-3.24)	<0.001	0.77 (0.30-1.92)	1.07 (0.60-2.30)	0.001

* p-value by Wilcoxon signed ranks test, median (IQR)

financial expenses for both patients and health authorities and shorten the duration of hospitalization.

In the present study, randomization appeared to produce similar demographic, baseline clinical and laboratory characteristics in the two groups. The overall treatment success rate assessed mainly on conversion of microbial CSF culture was 66.7%. No matter how high the success rate occurred in the present study, the authors could not guarantee favorable long term outcome. Maintenance phase of fluconazole can continue the condition of sustained cure. However, the factor most closely associated with relapse during the maintenance phase reported previously was no flucytosine in combination with amphotericin B during initial 2 weeks of therapy[11]. The combination therapy, which helps broadening the spectrum of anti-fungal activity and decreasing emergence of resistance has been proved for a higher cure rate and increased sterilization of the CSF[6,12]. The authors did not design the study to examine the susceptibility testing of *Cryptococcus neoformans*, which may express some resistance.

There was also no statistically significant difference in treatment success between both study groups ($p = 0.574$). Although some patients had only one culture negative and subsequent cultures could not be evaluated as patients were either lost to follow-up or died. Adding to unavailability of the combination therapy during the initial phase and design of the present study, was the fact that one-third of the patients (significantly higher proportion in the randomized 1-week treatment) had dropped out and were not available at the 10-week evaluation point, and therefore, there was considerable loss of information, particularly with regard to CSF sterilization as an end point. Although further extraction of the loss to follow-up groups could not show a significant change of the result in comparison, whether initial 1-week amphotericin B should be recommended in current clinical practice to require CSF sterilization before a switch to consolidation fluconazole therapy, is still not clear. Cryptococcal clearance in CSF was found highest during the first 2 weeks of therapy, in which CSF cryptococcal colony-forming unit counts decreased by > 5 logs[13,14]. In the present study the cumulative CSF culture clearance rate at two weeks was 24.6% (26.7% in AmB 1 and 22.2%in AmB2, $p = 0.935$). This rate was lower than those reported by Van der Horst et al and Pitisuttithum et al[6,10]. The points to emphasize were the optimal therapy selection and the suitable drug dose and duration. This should be driven by the knowledge of the clinicians and the needed and limited resources in health care.

Mortality rate for AIDS-associated acute cryptococcal meningitis ranged from 14% among patients receiving amphotericin B alone to > 25% among patients treated with azoles[4,8]. The overall mortality rate in the present study was 14%. The majority of deaths, 87.5% (7/8) occurred in the initial two weeks of treatment and the most probable cause of death was increased intracranial pressure. This mortality rate is lower than two previous studies from Thailand[10,15]. Higher deaths occurred in the AmB2 but were not statistically significant. There was no significant difference in the distribution of high risk groups between the two groups (Table 1) to explain the increased mortality in AmB2 however, 9 out of 15 (60%) patients in AmB1 were lost to follow-up during the first two weeks of therapy. These patients could have died of the disease after discharge, as deaths due to cryptococcal disease most likely occur during the first two weeks of treatment. This might have resulted in under estimation of the mortality rate in the present study; therefore this result should be interpreted with caution.

Nephrotoxicity including serum creatinine elevation, hypokalemia, hypomagnesemia and renal tubular acidosis has been reported in 30%-80% of patients given amphotericin B[16], 3% of who will have toxic side effects of a magnitude that requires it to be discontinued within the first 2 weeks of therapy[6]. In the present study, only 19.5% of patients and 10% of patients had serum creatinine elevation (≥ 2 mg/dL) at week 1 and week 2, respectively. 43.5% of patients and 31% of patients had hypokalemia ($K \leq 3.0$ meq/L) at week 1 and week 2, respectively. There was no significant difference of renal toxicity between both groups of treatment ($p = 0.534$ for creatinine elevation and $p = 0.498$ for hypokalemia). None of these patients required reduction of dosage or discontinuation. The reduced nephrotoxicity could be attributed to the use of saline during amphotericin B administration. There was no significant difference in nephrotoxicity between both groups of treatment and no significant change was detected among hematological indices during the present study.

The findings of comparable safety and efficacy between short course (1-week) and 2-week initial amphotericin B therapy represent an important step in identifying the optimal time for switching from intravenous amphotericin B to oral therapy to reduce hospital accommodation and health care budget. The authors realize that a small sample size is one of the limitations of the present study. In addition, CSF cryptococcal count was not performed to determine and ascertain

fungicidal activity of the two regimens. Therefore, a large-scale randomized trial with serial quantification of viable CSF cryptococci is recommended to validate the efficacy and safety of short-term (one-week) amphotericin B in the treatment of AIDS associated cryptococcal meningitis.

References

1. Mitchell TG, Perfect JR. Cryptococcosis in the era of AIDS - 100 years after the discovery of Cryptococcus neoformans. Clin Microbiol Rev 1995; 8: 515-48.
2. Powderly WG. Cryptococcal meningitis and AIDS. Clin Infect Dis 1993; 17: 837-42.
3. Tansuphasawadikul S, Amornkul PN, Tanchanpong C, Limpakarnjanarat K, Kaewkungwal J, Likanonsakul S, et al. Clinical presentation of hospitalized adult patients with HIV infection and AIDS in Bangkok, Thailand. J Acquir Immune Defic Syndr 1999; 21: 326-32.
4. Lyman CA, Walsh TJ. Systemically administered antifungal agents. A review of their clinical pharmacology and therapeutic applications. Drugs 1992; 44: 9-35.
5. Saag MS, Graybill RJ, Larsen RA, Pappas PG, Perfect JR, Powderly WG, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. Clin Infect Dis 2000; 30: 710-8.
6. van der Horst CM, Saag MS, Cloud GA, Hamill RJ, Graybill JR, Sobel JD, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. N Engl J Med 1997; 337: 15-21.
7. Ostrosky-Zeichner L, Marr KA, Rex JH, Cohen SH. Amphotericin B: time for a new "gold standard". Clin Infect Dis 2003; 37: 415-25.
8. Saag MS, Powderly WG, Cloud GA, Robinson P, Grieco MH, Sharkey PK, et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. The NIAID Mycoses Study Group and the AIDS Clinical Trials Group. N Engl J Med 1992; 326: 83-9.
9. Powderly WG. Therapy for cryptococcal meningitis in patients with AIDS. Clin Infect Dis 1992; 14(Suppl 1): S54-9.
10. Pitisuttithum P, Tansuphasawadikul S, Simpson AJ, Howe PA, White NJ. A prospective study of AIDS-associated cryptococcal meningitis in Thailand treated with high-dose amphotericin B. J Infect 2001; 43: 226-33.
11. Saag MS, Cloud GA, Graybill JR, Sobel JD, Tuazon CU, Johnson PC, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Clin Infect Dis 1999; 28: 291-6.
12. White M, Cirrincione C, Blevins A, Armstrong D. Cryptococcal meningitis: outcome in patients with AIDS and patients with neoplastic disease. J Infect Dis 1992; 165: 960-3.
13. Brouwer AE, Rajanuwong A, Chierakul W, Griffin GE, Larsen RA, White NJ, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. Lancet 2004; 363: 1764-7.
14. Brouwer AE, Teparrukkul P, Pinpraphaporn S, Larsen RA, Chierakul W, Peacock S, et al. Baseline correlation and comparative kinetics of cerebrospinal fluid colony-forming unit counts and antigen titers in cryptococcal meningitis. J Infect Dis 2005; 192: 681-4.
15. Imwidthaya P, Poungvarin N. Cryptococcosis in AIDS. Postgrad Med J 2000; 76: 85-8.
16. Fisher MA, Talbot GH, Maislin G, McKeon BP, Tynan KP, Strom BL. Risk factors for Amphotericin B-associated nephrotoxicity. Am J Med 1989; 87: 547-52.

การเปรียบเทียบการรักษาภาวะเยื่อหุ้มสมองอักเสบจากเชื้อคริปโตคอคคัสในผู้ป่วยเอดส์ด้วยสูตรยาแอมโฟเทอริซิน บี ระยะเวลา 1 สัปดาห์และ 2 สัปดาห์ ตามด้วยยาฟลูโคนาโซล

สมสิทธิ์ ตันสุภสวัสดิ์กุล, วิรัช เมฆอนันต์ธวัช, เบ็ญจลักษณ์ ผลรัตน์, ละม่อม บุญปก, อเนลเล เกตาฮัน, พรรณี ปิติสุทธิธรรม

หลักการ: *ภาวะเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอคคัสเป็นอาการนำที่พบได้บ่อยในกลุ่มผู้ป่วยเอดส์ที่ติดเชื้อฉกฉวยโอกาส ผู้ป่วยที่ได้รับการรักษาด้วยสูตรยามาตรฐานของยาแอมโฟเทอริซิน บี ต้องนอนโรงพยาบาล หรือมารับยาทางเส้นเลือดที่โรงพยาบาลทุกวัน ซึ่งต้องการความใส่ใจในเรื่องภาวะพิษจากการให้ยาดังกล่าว การให้ยาแอมโฟเทอริซิน บีระยะสั้นเป็นเวลา 1 สัปดาห์ จึงน่าจะเป็นทางเลือกที่ต้องการการประเมิน*

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบความปลอดภัยและประสิทธิภาพของการรักษาเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอคคัส ด้วยสูตรยา แอมโฟเทอริซิน บี ระยะสั้นเป็นเวลา 1 สัปดาห์ กับสูตรยาระยะเวลามาตรฐาน 2 สัปดาห์ และตามด้วยยาฟลูโคนาโซล*

วัสดุและวิธีการ: *ผู้ป่วยโรคเอดส์ที่มีภาวะเยื่อหุ้มสมองอักเสบจากการติดเชื้อราคริปโตคอคคัสเป็นครั้งแรก จำนวน 57 คน จะได้รับการคัดเลือกแบบสุ่มเพื่อการรักษาด้วยยา แอมโฟเทอริซิน บี 1 สัปดาห์ (AmB1) หรือ 2 สัปดาห์ (AmB2) และต่อด้วยยาฟลูโคนาโซลเป็นระยะเวลาอย่างน้อย 8 สัปดาห์ ผลการเพาะเชื้อราที่เปลี่ยนเป็นลบและการตอบสนองทางคลินิกหลังรักษาจะเป็นเป้าหมายปฐมภูมิและทุติยภูมิของการศึกษานี้ การติดตามอาการทางคลินิกและห้องปฏิบัติการในการศึกษานี้จะได้รับการประเมินในแง่ความปลอดภัยของการรักษา*

ผลการศึกษา: *ร้อยละ 63.8 และ ร้อยละ 70.4 ของผู้ป่วยเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอคคัสประสบความสำเร็จจากการรักษาแบบ AmB1 และ AmB2 ตามลำดับ ณ สัปดาห์ที่ 6 (p = 0.574) การประเมินทางคลินิกไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างการรักษาทั้ง 2 แบบ ณ สัปดาห์ที่ 10 สัดส่วนของผู้ป่วยที่เกิดภาวะพิษทางไตและภาวะอิเลกทรอไลท์ไม่สมดุลย์ในสูตรการรักษาทั้งสองแบบไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ อัตราการตายในการศึกษานี้ ณ สัปดาห์ที่ 10พบร้อยละ 14 โดยร้อยละ 75 ของผู้ป่วยที่เสียชีวิตได้รับสูตรยา AmB2*

สรุป: *ในการศึกษาครั้งนี้พบว่าผลการรักษาด้วยสูตรยาระยะสั้นให้ประสิทธิภาพไม่แตกต่างจากสูตรการรักษาแบบมาตรฐานในผู้ป่วยโรคเอดส์ที่มีเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอคคัส สูตรการรักษาระยะสั้นจึงอาจเป็นทางเลือกในการดูแลผู้ป่วยเพื่อลดภาระการครองเตียงและรายจ่ายของสถานบริการสาธารณสุขที่มีงบประมาณจำกัด*