AMPHOTERICIN B WITH OR WITHOUT FLUCYTOSINE FOLLOWED BY FLUCONAZOLE AS PRIMARY THERAPY FOR CRYPTOCOCCAL MENINGITIS IN PATIENTS WITH AIDS

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Abstract. Eighteen consecutive AIDS patients with a first episode of cryptococcal meningitis were enrolled in the study to evaluate the efficacy and tolerability of amphotericin B with or without flucytosine followed by fluconazole as primary therapy for cryptococcal meningitis in patients with AIDS. The treatment consisted of intravenous amphotericin B 0.6 mg/kg daily with or without flucytosine (150 mg/kg d in four divided doses) for 2 weeks which was then followed by oral fluconazole 400 mg daily for 8 weeks. After completion of primary therapy, all patients received a maintenance dose of oral fluconazole 200 mg daily. The primary therapy was successful in 17 (94%) of the 18 patients. The median length of time to the first negative cerebrospinal fluid culture for *Cryptococcus neoformans* in the 17 patients with successful treatment was 3 (range 2 to 6) weeks. No patient had to discontinue the treatment due to adverse drug reactions. During a mean observation period of 26.94 weeks, no relapse case was documented among the 17 patients. Our results indicate that this regimen as primary therapy for cryptococcal meningitis in AIDS patients is effective and well tolerated.

INTRODUCTION

Cryptococcal meningitis is the most common life-threatening opportunistic fungal disease in patients with acquired immunodeficiency syndrome (AIDS) (Dismukes, 1988). Approximately 10% of patients with AIDS develop cryptococcal meningitis during the course of their illness (Dismukes, 1988; Chuck and Sande, 1989) and the 12-month overall survival rate is 30-60% (Chuck and Sande, 1989; Saag *et al,* 1992). However, the survival rate of AIDS patients will improve over the next decade because of the widespread use of more effective antiretroviral therapy and prophylactic regimens to prevent the development of life-threatening opportunistic infections (Kaplan *et al,* 1995). Thus, the incidence of cryptococcal meningitis will probably increase as survival rates of patients with AIDS improve and the treatment of cryptococcal meningitis will become increasingly important.

Amphotericin B, either alone or combined with flucytosine, is the standard primary therapy for cryptococcal meningitis in patients with AIDS (Powderly, 1993). However, amphotericin B toxicities are frequently observed, especially nephrotoxicity. Furthermore, several patients develop fever, chill, rigors, nausea, vomiting or headache during the intravenous infusion of amphotericin B, and the administration of this drug requires the patients' hospitalization (Saag *et al,* 1992; Powderly, 1993). Fluconazole, a bis-triazole derivative, has been shown to be very effective against fungal infection caused by *Cryptococcus neoformans* (Grant and Clissold, 1990). It is the most attractive of the azoles for the treatment of cryptococcal meningitis in AIDS patients because of its excellent pharmacokinetic properties including good penetration into cerebrospinal fluid (CSF) and a long half-life. Moreover, this drug is well tolerated and the availability or oral form means that patients do not have to be admitted to hospital (Grant and Clissold, 1990). Previous study showed that fluconazole is an acceptable alternative to amphotericin B as primary therapy for cryptococcal meningitis in patients with AIDS (Saag *et al,* 1992).

We report our experience in an open-label trial of primary therapy for first episode cryptococcal meningitis in AIDS patients using amphotericin B with or without flucytosine for a short period of 2

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weeks followed by fluconazole for 8 weeks. The aim of this ongoing study is to evaluate the efficacy and tolerability of this treatment regimen.

MATERIALS AND METHODS

Patients with AIDS at Songklanagarind Hospital were enrolled in this open-label trial from July 1994 through December 1995 if they had clinical and CSF findings consistent with first episode cryptococcal meningitis. Clinical findings associated with cryptococcal infection of the CSF included headache, fever, stiff neck, seizures, altered mentation, etc. CSF findings consistent with cryptococcal meningitis included abnormal protein, glucose and white blood cell count and positive India ink preparation for *Cryptococcus*. Patients also had to have a positive culture for *C. neoformans* from CSF. Patients were excluded if they were younger than 15 years old or pregnant or lactating or considered unlikely to survive for more than 2 weeks (by clinical judgement of the investigator). They were also excluded if they had evidence of renal insufficiency (creatinine clearance rate <50 ml/minute), liver impairment (SGOT and SGPT >5 times the upper limit of normal), impaird bone marrow function (granulocyte count <1,250/mm^3 or platelet count <50,000/mm^3) or were found to have a concurrent central nervous system disease or psychiatric illness. During the treatment period, all patients were evaluated in terms of mental status, biocytochemical characteristics of CSF (protein levels, glucose concentration and white blood cell count), serum and CSF cryptococcal latex agglutination antigen test, India ink preparation and CSF culture for *Cryptococcus*. All patients gave their written informed consent to participate in this study.

Treatment consisted of the administration of intravenous amphotericin B 0.6 mg/kg daily infused over 4 hours with or without flucytosine (150 mg/kg/d in four divided doses) for 2 weeks, then followed by oral fluconazole 400 mg daily for 8 weeks. Complete blood counts, liver function tests, serum creatinine and electrolyte were monitored weekly for the first 4 weeks and every 4 weeks thereafter. After completion of primary therapy, all patients received a maintenance dose of oral fluconazole 200 mg daily.

Response to therapy was considered successful if patients achieved the resolution of the signs and symptoms of cryptococcal meningitis plus a negative CSF culture within 10 weeks. A lack of clinical improvement and/or the failure to clear *C. neoformans* from CSF by the end of 10 weeks was defined as a failure of treatment. Relapses were defined as the reemergence of clinical symptoms of cryptococcal meningitis and positive CSF culture after the primary therapy.

RESULTS

Eighteen consecutive patients with AIDS were enrolled in the study. Thirteen were males and five were females. Their mean age was 32.44 ± 7.69 (range 22 to 52) years and their mean weight was 47.79 ± 7.31 (range 35.5 to 68) kg. The median $CD4^+$ lymphocyte count was 50 (range 8 to 150)/mm^3. The clinical and laboratory features are summarized in Table 1. Eight patients had opportunistic infections other than cryptococcal disease: three had cytomegalovirus retinitis, one had histoplasmosis, one had pulmonary nocardiosis and hepes zoster involving the right hand, one had tuberculous lymphadinitis, one had tuberculous lymphadinitis and herpes zoster of left hand, and one had salmonellosis. Thirteen patients received amphotericin B alone and only five patients received amphotericin B with flucytosine in the first 2 weeks. Our treatment was successful in 17 (94%) of the total 18 patients. Only one patient failed to clear *C. neoformans* from CSF by the end of 10 weeks and received amphotericin B alone in the first 2 weeks. He was lost to follow-up after the end of primary therapy. The median length of time to the first negative CSF culture for *C. neoformans* in the 17 patients with successful treatment was 3 (range 2 to 6) weeks. CSF culture for *C. neoformans* and cryptococcal antigens during the primary therapy in 18 patients are shown in Tables 2 and 3, respectively.

Until December 1995 (mean observation period 26.94 ± 19.43 weeks), no relapse case was documented among the 17 patients. Three patients died: one of these deaths was due to hypovolemic shock from upper gastrointestinal hemorrhage, one was due to suicide and one was due to wasting syndrome. Three patients were lost to follow-up at weeks 10, 10 and 11. Twelve patients are still alive

Table 1

Clinical and laboratory features of 18 AIDS patients with cryptococcal meningitis.

Features			Number of patients (%)
Signs or symptoms			
fever			17 (94.44)
headache			15 (83.33)
stiff neck			9 (50)
seizure			3 (16.66)
papilledema			2 (11.11)
stuporous			2 (11.11)
diplopia			1 (5.55)
internuclear ophthalmoplegia			1 (5.55)
blurred vision			1 (5.55)
blindness			1 (5.55)
facial palsy			1 (5.55)
Extraneural cryptococcal infections			
blood			4 (22.22)
prostatic secretion			4 (22.22)
bone marrow			1 (5.55)
liver			1 (5.55)
skin			1 (5.55)
Lumbar puncture			
pressure :	< 20 cmH20		7 (38.89)
	≥ 20 cmH20		11 (61.11)
WBC count :	< 20/mm^3		14 (77.78)
	≥ 20/mm^3		4 (22.22)
protein :	< 45 mg/dl		8 (44.44)
	≥ 45 mg/dl		10 (55.56)
glucose in CSF/serum :	< 0.5		9 (50)
	≥ 0.5		9 (50)
India ink preparation :	positive		18 (100)
	negative		0 (0)
CSF cryptococcal-antigen titer :	< 1:1,024		5 (27.78)
	≥ 1:1,024		13 (72.22)
Serum cryptococcal-antigen titer :	< 1:1,024		15 (83.33)
	≥ 1:1,024		3 (16.67)

(mean follow-up period 27.75 ± 15.77; range 10 to 57 weeks). No patients had to discontinue the treatment due to adverse drug reactions. During amphotericin B treatment in the first two weeks, there were only mild and reversible adverse drug reactions, including fever with chill, headache, nausea, vomiting and electrolyte imbalance. No adverse drug reaction was observed during fluconazole treatment. However, because of several coadministered medications in these AIDS patients, identifying antifungal-induced drug reactions was difficult.

DISCUSSION

A previous study by Saag *et al* (1992) showed that fluconazole is an acceptable alternative to amphotericin B as primary therapy for cryptococcal

Table 2
CSF culture for *C. neoformans* during the 10 weeks of primary therapy in 18 AIDS patients with cryptococcal meningitis.

	Week									
Subject	1	2	3	4	5	6	7	8	9	10
1	+	+	+	nd	+	-	nd	nd	nd	-
2	+	nd	+	+	-	-	nd	nd	nd	-
3	+	+	+	-	-	nd	nd	nd	nd	-
4	+	-	-	nd	nd	nd	nd	nd	nd	-
5	+	-	-	nd	nd	nd	nd	nd	nd	-
6	+	-	-	nd	-	nd	nd	-	nd	-
7	+	+	+	-	-	-	nd	nd	nd	-
8	+	+	nd	+	-	-	nd	nd	nd	-
9	+	+	+	-	-	nd	nd	nd	nd	-
10	+	+	+	nd	nd	nd	+	nd	nd	+
11	+	-	-	nd	nd	nd	nd	nd	nd	-
12	+	-	-	nd	nd	nd	nd	-	nd	-
13	+	-	-	nd	-	nd	nd	nd	nd	-
14	+	-	-	nd	nd	nd	nd	-	nd	-
15	+	+	-	nd	-	nd	nd	-	nd	-
16	+	-	-	nd	-	nd	nd	nd	nd	-
17	+	+	-	-	nd	nd	nd	nd	-	-
18	+	-	-	nd	-	-	nd	nd	nd	-

+ = positive CSF culture for *C. neoformans*, - = negative CSF culture for *C. neoformans*, nd = not done

Table 3
CSF cryptococcal antigens during the 10 weeks of primary therapy in 18 AIDS patients with cryptococcal meningitis.

	Week									
Subject	1	2	3	4	5	6	7	8	9	10
1	1:5,120	1:2,560	1:1,280	nd	nd	nd	nd	nd	nd	1:320
2	1:640	nd	nd	1:320	nd	1:80	nd	nd	nd	1:80
3	1:2,560	1:2.560	1:1,280	nd	nd	nd	nd	nd	nd	1:80
4	1:5,120	1:5,120	nd	nd	nd	nd	nd	nd	nd	1:80
5	1:1,280	nd	nd	nd	nd	nd	nd	nd	nd	1:80
6	1:320	1:640	1:640	nd	1:320	nd	nd	1:10	nd	1:10
7	1:2,560	nd	nd	nd	1:2,560	nd	nd	nd	nd	1:320
8	1:10	nd	nd	nd	nd	nd	nd	nd	nd	0
9	1:2,560	1:160	1:20	nd	nd	nd	nd	nd	nd	nd
10	1:320	nd	nd	nd	nd	nd	nd	nd	nd	1:10
11	1:1,280	1:1,280	nd	nd	nd	nd	nd	nd	nd	0
12	1:2,560	nd	nd	nd	nd	nd	nd	1:640	nd	nd
13	1:1,280	nd	1:640	nd	1:320	nd	nd	nd	nd	1:160
14	1:5,120	1:2,560	nd	nd	nd	nd	nd	nd	nd	nd
15	1:1,280	1:160	1:160	nd	nd	nd	nd	nd	nd	nd
16	1:5,120	nd	1:1,280	nd	nd	1:80	nd	nd	nd	nd
17	1:2,560	nd	nd	1:640	nd	nd	nd	nd	1:80	nd
18	1:640	nd	1:320	nd	nd	1:80	nd	nd	nd	nd

nd = not done

meningitis in AIDS patients and there was no significant difference between the amphotericin B group and the fluconazole group in overall mortality due to cryptococcosis. However, mortality during the first two weeks of therapy was higher in the fluconazole group. This may have been due to the longer time to the first negative CSF culture in the fluconazole group when compared with the amphotericin B group. In addition, the success rate for single-drug therapy with either amphotericin B or fluconazole in this study was disappointingly low, 40% and 34%, respectively (Saag *et al,* 1992). This may have been due to the low dosage of both drugs. Recently, Lalla *et al* (1995) showed that an aggressive approach to the primary treatment of cryptococcosis in AIDS patients with the administration of a relatively high dose of amphotericin B (1 mg/kg/d) for a relatively short peroid was effective, with a treatment success rate of more than 90%, but this regimen still had severe adverse drug reaction: nephrotoxicity developed as a result of amphotericin B administration, 22.6%. Therefore, we proposed to use amphotericin B as an initial agent for a short peroid of 2 weeks and fluconazole for another 8 weeks as primary therapy for cryptococcal meningitis in AIDS patients and the dosages of both drugs in this treatment regimen were higher than those of Saag *et al* (1992). To our knowledge, no experience has previously been reported with the use of this treatment regimen as the primary therapy for cryptococcal meningitis in AIDS patients. Our results showed a high success rate together with a rapid mycologic and serologic response of the CSF to the treatment, even though the majority of our patients were at high risk of a poor outcome. Moreover, all patients who received flucytosine in the first 2 weeks responded very well to this treatment regimen. However, the efficacy of flucytosine as the treatment for cryptococcal meningitis can not be concluded from our study because of a small number of patients.

This treatment regimen was well tolerated; there were only minor amphotericin B-related drug reactions without nephrotoxicity, and no patients had to discontinue the treatment. In addition, the availability of oral fluconazole, which can be administered for long-term therapy without adverse drug reaction, had reduced the need for hospitalization. During the follow-up period after the end of primary therapy, we continued maintenance treatment with oral fluconazol 200 mg daily and no relapse case was documented. Therefore, our results seem to support the use of amphotericin B followed by fluconazole as the primary treatment for cryptococcal meningitis in AIDS patients. However, our study included only a small number of patients and a further large prospective study is required to confirm the efficacy and tolerability of this treatment regimen.

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