CASE REPORT

TREATMENT OF CRYPTOCOCCAL MENINGITIS WITH TRIPLE COMBINATION OF AMPHOTERICIN B, FLUCYTOSINE AND ITRACONAZOLE

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Cryptococcal meningitis is a serious neurological disease which is caused by a yeast-like organism, *Cryptococcus neoformans*. Amphotericin B with or without flucytosine continues to be the standard therapeutic regimen with a success rate about 70% (Diamond and Bennett, 1974; Bennett *et al*, 1979; Hay *et al*, 1980; De Wytt *et al*, 1982; Dismukes *et al*, 1987; Sugar *et al*, 1990). The discovery of the antifungal triazoles (itraconazole, fluconazole) represents an advance in the treatment of cryptococcal meningitis. Clinical trials in patients with cryptococcal meningitis have indicated that the triazoles are effective as either initial or maintenance therapy with minimal side effect (Sugar *et al*, 1990; Como and Dismukes, 1994). However, these regimens had failed to treat some patients with cryptococcal meningitis. Also, certain patients who had failed with conventional treatment, responded to itraconazole and vice versa (Viviani *et al*, 1987; Denning *et al*, 1989; Chotmongkol and Jitpimolmard, 1992; 1993).

In this paper we report the results of an open study concerning treatment in non-AIDS patients with cryptococcal meningitis with triple combination of amphotericin B, flucytosine and itraconazole.

Nine patients fulfilled the following entry criteria : (1) proven cryptococcal meningitis based on one of the following: a) a positive cerebrospinal fluid (CSF) Indian ink preparation or culture for *C. neoformans*; b) CSF findings were compatible with cryptococcal meningitis plus one of the following : a positive latex agglutination test for cryptococcal antigen in serum or CSF, a positive culture or a histopathologic study from an extreneural site, or a positive histopathologic evidence of central nervous system cryptococcosis; (2) life expentancy of at least one week after initiation of treatment; (3) age of more than 16 years.

Clinical response was assessed by a combination of symptoms, fever and physical findings. Culture response was assessed by weekly fungal cultures of previously positive site. Serologic response was assessed by repeated measurement of CSF cryptococcal antigen titer after treatment. Possible toxicity was assessed by patient interviews and by measurement at weekly interval of the following : hematologic parameters, serum electrolytes, BUN, creatinine, glucose, liver function tests and urinalysis.

All patients received intravenous amphotericin B (0.3 mg/kg/day), oral flycytosine (150 mg/kg/day in four divided doses) and itraconazole (400 mg per day orally twice a day). Until mycological cultures disclosed nothing, then itraconazole 400 mg per day was ad-ministrated alone through eight weeks of treatment.

The following definitions of clinical efficacy were used : (1) Cure, defined as disappearance of all pre-treatment signs and symptoms of cryptococcal meningitis; (2) Improvement, defined as improvement or partial disappearance of pre-treatment signs and symptoms; (3) Failure, defined as no change in or worsening of pre-treatment signs and symptoms; (4) Relapse, defined as eradication of pre-treatment pathogen followed by its reappearance.

From October 1993 to April 1994, nine cases were included in the study. There were five males and four females. Age incidence ranged from 20-77 years with a mean of 57 years. All of them had positive CSF Indian ink staining, culture and cryptococcal antigen for *C. neoformans*, except patient no. 1, 3 had negative Indian ink stain and patient no. 7 had negative both Indian ink stain and CSF culture (Table 2). The clinical manifestations and clinical outcome are shown in Table 1. Associated condition was found in 1 case (lymphoma with chemotherapy in patient

Table 1
Patient characteristic and clinical outcome.

Patient no.	Age/sex	History	Physical examination	Other foci of infection	Outcome
1	61/F	Fever and headache 10 days, stuporous 1 day	T 38.5°C, stiffneck	-	cure
2	57/F	Fever and headache 2 months	T 38.9°C, stiffneck, papilledema	lung	cure with relapse
3	77/M	Mental change 3 weeks, semicoma 1 week	stiffneck	-	cure
4	73/F	Fever and headache 6 weeks, convulsion and confusion 1 week	T 38.5°C, stiffneck, mild paraplegia	lung	cure
5	68/F	Fever and headache 2 months, drowsiness 2 weeks, semicoma 4 days	T 39.5°C, stiffneck	-	died
6	20/M	Fever and headache 2 weeks	T 39.0°C, stiffneck	-	improvement but died from lymphoma
7	70/M	Headache and confusion 4 days	T 38.5°C, stiffneck, paraplegia grade II with urinary retention	-	cure
8	38/M	Headache 3 months, fever 1 month	T 39.0°C, stiffneck, bilateral 6th N, palsy, papilledema	-	cure
9	53/M	Fever and headache 1 week	T 39.0°C, stiffneck, papilledema	-	cure

no.6). Three patients (patient no. 2, 8, 9) had high initial opening CSF pressure (> 300 mmH_2O). CT scan of brain demonstrated hydrocephalus in 4 cases (marked hydrocephalus in patient no. 1, 4, 5 and mild hydrocephalus in patient no. 3) and normal findings in 5 cases. Ventriculostomy was performed in patient no.1 and 5 and a post-operative large intracerebral hematoma occurred in patient no. 5. Clinical assessment demonstrated cure in seven cases. Of the patient no. 5, neurological symptoms were not improved and died from hospital-acquired infection. Of the patient no. 6, symptoms of meningitis were improved but he died from lymphoma.

Table 2 demonstrates the CSF results before and during treatment. Eradication of positive CSF Indian ink stain and cultures occurred within one to two weeks after treatment. Severe side effects and toxicity were not observed except chills and hypokalemia from amphotericin B.

The patients were observed with a mean of 7 months after completion of treatment. There was only one patient who had a relapse (patient no. 2). The symptoms and signs, including CSF abnormalities, occurred 3 months after completion of treatment. Retreatment with the same regimen was successful.

Table 2

CSF results before and during therapy.

Patient	Indian ink stain		Culture		Cryptococcal antigen*	
no.	initial	time until stain became negative, wk	initial	time until culture became negative, wk	initial	after therapy
1	-	-	+	1	1:1	1:1
2	+	2	+	2	1:1,000	1:1,000
3	-	-	+	1	1:100	1:10
4	+	1	+	1	1: ≥ 10,000	-
5	+	1	+	1	1: ≥ 10,000	ND
6	+	2	+	2	1:100	ND
7	-	-	-	-	1:10	-
8	+	2	+	2	1:100	1:10
9	+	2	+	2	1: ≥ 10,000	1:10

* Cryptococcal antigen titer was diluted by 1:1, 1:10, 1:100, 1:1,000 and ≥ 1:10,000.
+ = positive, - = negative, ND = not done because the patient died at the 5th week and 4th week after treatment.

The present study has documented the efficacy of intensive treatment with combination of amphotericin B, flucytosine and itraconazole in patient with cryptococcal meningitis. The advantage of this regimen is to reduce both the serious side effects of amphotericin B in combination with flucytosine and the hospital-days, and the cost of treatment is less. Interestingly, no patient failed to respond to this regimen and rate of negative Indian ink staining and CSF culture for *C. neoformans* was rapid. From these clinical data and our previous experience we suggest that this intensive regimen is highly effective in the treatment of cryptococcal meningitis.

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