Clinical Characteristics and Outcomes of Patients with Cryptococcal Meningoencephalitis in a Resource-Limited Setting

Methee Chayakulkeeree MD, PhD*,
Pattaraporn Wangchinda MD*

The authors contribute equally to this manuscript
** Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Background: *Cryptococcosis is a potentially lethal opportunistic infection among human immunodeficiency virus (HIV)-infected individuals. The mortality rate of patient with cryptococcal meningoencephalitis (CM) in Thailand is high. Studying the factors associated with treatment failure is important to improve outcome.*
Material and Method: *A retrospective study of patients with cryptococcosis in Siriraj Hospital, Thailand, during 2005-2008 was conducted. Treatment options, outcomes, survival and factors associated with outcomes and mortality were analyzed.*
Results: *A total of 143 patients with cryptococcosis were enrolled. Mean age was 39 years old and 58.7% were male. There were 124 HIV-infected patients (86.7%) and 116 of those had CM. Favorable clinical response in HIV-associated CM was 55.2% and 6-month survival was 67.2%. Relapse was found in 21 patients (18.1%). Factors associated with favorable clinical response included lower opening and closing pressures and a higher white blood cell in cerebrospinal fluid (CSF). Favorable mycological response was 56.8% and factors associated with favorable mycological response were a lower CD_4^+ T-lymphocyte count and a longer amphotericin B treatment. The median time to achieve CSF sterilization was 30 days. Factors associated with survival were a longer course of amphotericin B, a lower CSF opening pressure and a higher white blood cell in CSF.*
Conclusion: *High mortality rate of HIV-associated CM was demonstrated and most likely linked to inadequate induction antifungal therapy resulting in inability to sterilize CSF. New strategies and/or guidelines are suggested to improve survival.*

Keywords: *Cryptococcus neoformans, Cryptococcosis, Cryptococcal meningoencephalitis, Predicting factors, Cryptococcal infection*

J Med Assoc Thai 2014; 97 (Suppl. 3): S26-S34
Full text. e-Journal: *http://www.jmatonline.com*

Cryptococcosis is an important opportunistic infection in immunocompromised individual, especially those with human immunodeficiency virus (HIV) infection[1]. It is the third most common opportunistic infection in patients with acquired immune deficiency syndrome (AIDS) in Thailand following tuberculosis and pneumocystis pneumonia[2]. Although antiretroviral treatment has become more easily accessible during the last decade, resulting in a significant reduction of opportunistic infections in such patients[3], the incidence of cryptococcosis in AIDS is still as high as 13.5%[2]. In addition, the incidence of cryptococcosis among non-HIV immunocompromised individuals has not decreased[4]. Cryptococcosis is also an important cause of graft rejection and mortality in patients with organ transplantation[5]. Clinical manifestations of cryptococcal infection include meningoencephalitis, pulmonary cryptococcosis and disseminated disease. Detection of cryptococcal polysaccharide by latex agglutination assay and fungal cultures from blood and cerebrospinal fluid (CSF) are the main tests for diagnosis of cryptococcal infections[6].

The 2010 Clinical Practice Guidelines for Management of Cryptococcal Diseases issued by Infectious Diseases Society of America recommended that a combination of amphotericin B and flucytosine (5-FC) be used as first line antifungal therapy during induction phase for cryptococcosis[7]. After two weeks of induction, the combination of amphotericin B and 5-

Correspondence to:
Chayakulkeeree M, Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Prannok Road, Bangkoknoi, Bangkok 10700, Thailand.
Phone: 0-2419-9462, Fax: 0-2419-7783
E-mail: methee.cha@mahidol.ac.th

FC can be replaced by oral fluconazole for another 8 weeks of consolidation treatment. If amphotericin B is used as monotherapy during the induction period, a longer period (4-6 weeks) of amphotericin B is recommended before changing to fluconazole.

However, 5-FC is not available in Thailand and amphotericin B monotherapy is the only standard treatment for patients with cryptococcal meningoencephalitis during the induction phase for two weeks, before switching to oral fluconazole[8-11]. Nevertheless, clinical characteristics and treatment outcomes of patients with cryptococcal meningoencephalitis in our hospital have never been evaluated. There is insufficient data to prove whether a 2-week course of induction amphotericin B monotherapy is equivalent to a longer course. Therefore, the objective of this study is to assess the clinical characteristics and factors related to treatment outcomes of patients with cryptococcal meningoencephalitis in a resource-limited setting where 5-FC is not available.

Material and Method

A retrospective chart review of patients older than 15 years with cryptococcosis (International Classification of Diseases, Tenth Revision, Clinical Modification; ICD10, code B45) who were admitted to Siriraj Hospital during 2005-2008 was conducted. Patients enrolled to this study must have a positive *Cryptococcus* spp. culture from clinical specimens, or a positive cryptococcal antigen from blood or CSF. Clinical characteristics, laboratory findings and treatment outcomes were collected and analyzed. Patients' characteristics included age, sex, underlying diseases, CD_4^+ T-lymphocyte counts, organ involvement of cryptococcosis, imaging results, clinical response and microbiological response. Laboratory results included fungal culture and cryptococcal antigen. Duration and dose of the antifungal agents were also collected. Complication, relapse and mortality within 6 months of the disease were also assessed. This study was approved by Siriraj Institutional Review Board (SIRB).

There were 4 outcomes to be evaluated, including clinical response, mycological response, relapse and 6-month mortality. Clinical response was defined by evidence of clinical improvement, defervescence, decrease in severity of headache or improvement of CSF profile without any complication. Mycological response was defined by evidence of negative CSF culture during antifungal treatment. Relapse was defined by presence of all of the followings during the first 6 months of diagnosis: (1) a previous laboratory confirmed case of cryptococcal infection (2) India ink, antigen test and/or culture positive for *C. neoformans* (3) no alternative diagnosis, provided that there had been a resolution of symptoms and culture before the event. Mortality rate at 6-month was defined by all cause mortality during the first 6 months after diagnosis of cryptococcosis.Factors associated with outcomes to be evaluated were patients' age, sex, CD_4^+T-lymphocyte counts and percent, presence of fungemia, dose and duration of amphotericin B during initial treatment, CSF pressure and profile on admission and two weeks after treatment.

Statistical analysis

For continuous variables, mean (standard deviation) or median (range) was described and comparison between the two outcomes was performed using independent Student's t-test or Mann-Whitney U test, depending on the distribution of data. For discrete variables, proportion as in percentage was presented and comparison between two outcomes was performed using Chi-square or Fisher's exact test as appropriate. Time to relapse was defined by the duration from the first day of induction therapy to relapse and time to death was defined by the duration from the first day of induction therapy to death.

Results

A total of 143 patients with cryptococcosis were enrolled. Patients' characteristics are shown in Table 1. Mean age was 39 years old, 84 (58.7%) were male and 124 (86.7%) were HIV-infected. Fungemia was found in 49.7%. Six patients were apparently immuno competent. Serum cryptococcal antigen was tested in 96 patients and 93 (96.9%) were positive. The ratio of non-HIV/HIV was highest in pulmonary cryptococcosis, whereas most patients with CNS and disseminated diseases were HIV-positive.

There were 116 patients with HIV-associated cryptococcal meningoencephalitis and patients' information is shown in Table 2. Cryptococcosis was the first manifestation of HIV infection in 51 (44%) patients. Forty (34.5%) and 19 (16.4%) patients had a history of tuberculosis and pneumocystis pneumonia, respectively. Median duration of known HIV infection was 2 months and median CD_4^+ T-lymphocyte count was 21 cells/mm^3. There were 13 patients developed cryptococcosis during antiretroviral therapy with one patient having a viral suppression. Fungemia was found in 58 (50%) patients. Favorable clinical response during

Table 1. Clinical characteristics of patients with cryptococcosis

Patients' characteristics	n = 143
Male, n (%)	84 (58.7)
Age mean ± SD	39±11
Median (min, max)	37 (21,85)
HIV, n (%)	124 (86.7)
Underlying diseases in non-HIV, n (%)	19 (13.3)
No underlying disease	6
Systemic lupus erythematosus	4
Diabetes mellitus	2
Immune thrombocytopenic purpura	2
Myasthenis gravis	1
Idiopathic low CD_4^+ lymphocyte	2
Thalassemia	1
Hematologic malignancy	1
Fungemia, n (%)	71 (49.7)
Positive serum cryptococcal antigen (n = 96), n (%)	93 (96.9)
Organ involvement	
Disseminated	69 (48.3%)
HIV/non-HIV	64/5
CNS	127 (88.8%)
HIV/non-HIV	116/11
Pulmonary	15 (10.5%)
HIV/non-HIV	8/7
Skin	2 (1.4%)
HIV/non-HIV	1/1

Table 2. Clinical characteristics of patients with HIV-associated cryptococcal meningoencephalitis

Patients' characteristics	n = 116
Newly diagnosed HIV infection, n (%)	51 (44)
Duration of HIV infection (months)	
Mean ± SD	25±46
Median (range)	2 (0,204)
CD_4^+ count (cells/mm^3)	
Mean ± SD	36±46
Median (range)	21 (1-371)
CD_4^+ percent (%)	
Mean ± SD	4.47±4.08
Median (range)	3.06 (0.27-23.74)
Previous tuberculosis, n (%)	40 (34.5)
Previous PCP, n (%)	19 (16.4)
Receiving HAART, n (%)	13 (11.2)
Duration of HAART (months)	
Mean ± SD	21±52
Median (range)	4 (2-192)
Evidence of HIV suppression, n (%)	1 (7.7)
Fungemia, n (%)	58 (50)
Positive serum cryptococcal Ag (n = 81), n (%)	79 (97.5)
Outcomes	
Favorable clinical response at 2 weeks, n (%)	64 (55.2)
6-month survival, n (%)	78 (67.2)

the first 2 weeks of induction therapy was 55.2% and 6-month survival was 67.2%. Table 3 revealed the treatment of patients with HIV-associated cryptococcal meningoencephalitis. Amphotericin B monotherapy was used for induction treatment in 99.1% and fluconazole was mainly used for consolidation and maintenance therapy. Median duration of amphotericin B treatment during induction therapy was 14 days.

Favorable clinical response during the first two week of induction therapy was achieved in 64 (55.2%) in HIV-associated cryptococcal meningoencephalitis. Factors associated with favorable clinical response included lower opening and closing pressures, and a higher white blood cell in CSF (Table 4). Overall mycological response was evaluable in 81 patients and 46 (56.8%) patients demonstrated a favorable outcome. Factors associated with favorable mycological response included lower CD_4^+T-lymphocyte count and a longer amphotericin B treatment (30 vs. 14.5 days) as shown in Table 5. The median time to achieve CSF sterilization was 30 days (95% confidence interval; 20.9, 39.1) as shown in the survival analysis in Fig. 1. Relapse was found in 21 (18.1%) out of 116 patients and those patients had a history of receiving a longer course of amphotericin B (Table 6). There were 78 (67.2%) patients surviving at 6 month after diagnosis and factors associated with survival included a longer course of amphotericin B, a lower CSF opening pressure and a higher white blood cell in CSF (Table 7). However, multivariate analysis did not show any factors that associated with clinical response, mycological response, relapse and survival due to inadequate sample size. Survival analysis for 6-month survival is shown in Fig. 2.

Discussion

Our results suggested that caring for patients with cryptococcal meningoencephalitis in a resource-limited setting needs to be improved. With amphotericin B induction monotherapy, there were only half of the patients that favorably responded to treatment and 32.8% of patients died within 6 months. However, most of our patients with cryptococcosis were HIV-infected and the majority was meningoencephalitis and

Table 3. Treatment of patients with HIV-associated cryptococcal meningoencephalitis

Treatment	n = 116
Induction therapy (n = 116)	
Amphotericin B, n (%)	115 (99.1)
Fluconazole, n (%)	1 (0.9)*
Amphotericin B dose (mg/kg/day)	
Mean ± SD	0.87±0.14
Median (range)	1 (0.5-1)
Duration of induction phase (days)	
Mean ± SD	19±23
Median (range)	14 (1-226)*
Consolidation therapy (n = 87)	
Fluconazole, n (%)	79 (90.8)
Amphotericin B, n (%)	6 (6.9)
Itraconazole, n (%)	2 (2.3)
Fluconazole dose during consolidation (mg/day)	
Mean ± SD	438±121
Median (range)	400 (200-800)
Duration of consolidation (days)	
Mean ± SD	80±65
Median (range)	60 (7-356)
Maintenance therapy (n = 53)	
Fluconazole, n (%)	53 (100)
Fluconazole dose during maintenance (mg/day)	
Mean ± SD	215±53
Median (range)	200 (200-400)

* one patient received fluconazole as induction therapy for 226 days

disseminated disease. The 6-month mortality among our patients with HIV-associated cryptococcal-meningoencephalitis was comparable to those of other Asian countries. A study in Taiwan involved 88 patients of cryptococcal meningitis revealed mortality rates of 23.9% and 31.8% at 30 and 90 days, respectively[12]. However, only 42% were HIV-infected and the mortality was not different between patients with and without HIV infection. A study of 30 HIV-infected patients with cryptococcal meningitis in India showed a mortality of 36.7% and a low GCS score, papilledema, elevated CSF opening pressure (>250 mm of H_2O) and lack of regular HIV care were associated with poor outcome. In addition, CSF pleocytosis was significantly higher in the mortality group[13]. In rural South Africa, the inpatient mortality in 74 patients with HIV-associated cryptococcal meningitis was as high as 40.5% and only 10.8% were alive after 2 years with antiretroviral therapy[14].

Some patients in our study received induction amphotericin B treatment for more than 14 days. Although these patients had a higher rate of mycological response, they had a greater relapse rate. These findings are most likely due to more severe clinical manifestations in such patients influencing the clinicians to prolong induction therapy.

Combination to amphotericin B with 5-FC has been shown to improve clinical and mycological response in previous studies[15-17]. However, amphotericin B monotherapy was used as induction therapy because 5-FC has not been available in Thailand. Our results revealed that 44.8% had unfavorable clinical outcome and 43.2% demonstrated microbiological failure. A recent cohort study with 208 HIV-positive and HIV-negative patients with cryptococcal meningoencephalitis clearly showed that amphotericin B plus flucytosine for14 days as induction treatment resulted in a 26% failure rate compared with a 56% failure rate found in other regimens. In addition, mycological failure was lower in patients receiving amphotericin B plus flucytosine compared with those with other regimens (23% vs. 47%). Furthermore, less than 14 days of flucytosine treatment was also independently associated with treatment failure at 3

Table 4. Factors associated with clinical response in patients with HIV-associated cryptococcal meningoencephalitis

	Clinical response			
	Evaluable subject total = 116	Favorable n = 64	Unfavorable n =52	p-value
Age (year), mean ± SD	116	38±9	39±9	0.673
Female, n (%)	116	27 (42.2)	15 (28.8)	0.137
Fungemia, n (%)	116	30 (46.9)	28 (53.8)	0.459
CD4+ count (cells/mm^3), median (min, max)	115	29 (1, 222)	19 (2, 371)	0.175
Amphotericin B dose (mg/kg/day), mean ± SD	115	0.88±0.14	0.87±0.14	0.770
Amphotericin B duration (day), median (min, max)	116	14 (10, 226)	14 (1, 80)	0.197
Pre-treatment CSF parameters				
Opening pressure (cmH_2O), median (min, max)	112	23 (3, 60)	28 (12, 60)	0.005*
Closing pressure (cmH_2O), median (min, max)	100	12 (1, 32)	15 (1, 42)	0.023*
Protein (mg/dL), median (min, max)	112	65 (22, 377)	60 (16, 580)	0.077
Sugar (mg/dL), median (min, max)	112	41 (1, 69)	43 (5, 76)	0.834
WBC (cells/mm^3), median (min, max)	113	10 (1, 2,460)	2 (1, 6,240)	0.020*
End of induction (14 days) CSF parameters				
Opening pressure (cmH_2O), median (min, max)	38	16 (3, 30)	24 (5, 40)	0.218
Closing pressure (cmH_2O), median (min, max)	36	11 (3, 19)	10 (5, 19)	0.859
Protein (mg/dL), median (min, max)	47	62 (17, 536)	66 (29, 427)	0.424
Sugar (mg/dL), median (min, max)	47	45 (5, 82)	41 (7, 73)	0.405
WBC (cells/mm^3), median (min, max)	47	13 (1, 132)	9 (1, 177)	0.828

Table 5. Factors associated with mycological response in patients with HIV-associated cryptococcal meningoencephalitis

	Mycological response			
	Evaluable subject total = 81	Favorable n = 46	Unfavorable n = 35	p-value
Age (year), mean ± SD	81	40±10	39±10	0.6
Female, n (%)	81	20 (43.5)	15 (42.9)	0.96
Fungemia, n (%)	81	22 (47.8)	23 (65.7)	0.11
CD4+ count (cells/mm^3), median (min, max)	74	20 (5, 742)	29 (12, 583)	0.045*
Amphotericin B dose (mg/kg/day), mean ± SD	80	0.90±0.18	0.83±0.16	0.07
Amphotericin B duration (day), median (min, max)	81	30 (14, 54)	14.5 (12, 17)	<0.001*
Pre-treatment CSF parameters				
Opening pressure (cmH_2O), median (min, max)	70	32 (12, 60)	52 (14, 60)	0.727
Closing pressure (cmH_2O), median (min, max)	63	17 (10, 30)	26 (13, 45)	0.683
Protein (mg/dL), median (min, max)	71	67 (30, 179)	52 (37, 82)	0.076
Sugar (mg/dL), median (min, max)	71	45 (5, 61)	36 (26, 48)	0.944
WBC (cells/mm^3), median (min, max)	72	116 (1, 6,240)	35 (1, 700)	0.077
End of induction (14 days) CSF parameters				
Opening pressure (cmH_2O), median (min, max)	29	27 (5, 40)	8 (3, 30)	0.193
Closing pressure (cmH_2O), median (min, max)	27	11 (5, 19)	7 (3, 11)	0.189
Protein (mg/dL), median (min, max)	39	57 (20, 139)	76 (41, 202)	0.135
Sugar (mg/dL), median (min, max)	39	32 (7, 75)	36 (13, 46)	0.070
WBC (cells/mm^3), median (min, max)	39	9 (1, 177)	14 (2, 72)	0.793

months in this study[17]. Successful fungicidal antifungal regimens to sterile CSF at 2 weeks of induction therapy have been linked to favorable outcomes[18]. Our treatment outcome and mycological response were comparable to those treated with regimens without 5-FC in the previous studies. Therefore, the relatively higher mortality of our patients could be caused by a failure to sterilize CSF due to inadequate treatment. To support of this, the survival analysis also showed that 50% of our patients achieved CSF sterilization at 30 days (95% CI = 20.9, 39.1 days). Therefore, a 2-week treatment of amphotericin B was unlikely to sterilize the CSF in patients with cryptococcal meningoencephalitis. Other treatment options or guidelines are therefore warranted to improve outcomes and survival in our patients. In the situation without 5-FC, either prolonge damphotericin B induction treatment or in combination with high-dose fluconazole should be considered.

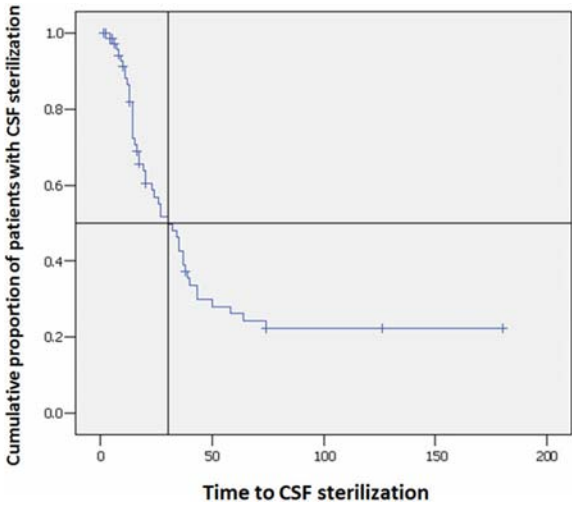

Fig. 1 Survival analysis for time to CSF sterilization in patients with HIV-associated cryptococcal meningoencephalitis (n = 81).

The present study revealed that a longer induction treatment of amphotericin B was associated with a higher 6-month survival, whereas a higher opening CSF pressure and a lower white blood cell counts were poor prognostic factors in our study. This evidence may be used as a guide to decide whether prolonged treatment of amphotericin B should be considered during induction period, in particular patients with high CSF opening pressure and low CSF white blood cell counts.

The limitation of this study is that it is a

Table 6. Factors associated with relapse in patients with HIV-associated cryptococcal meningoencephalitis

	Relapse of disease			
	Evaluable subject total = 116	Yes n = 21	No n = 95	p-value
Age (year), mean ± SD	116	39±7	38±9	0.609
Female, n (%)	116	2 (9.5)	40 (42.1)	0.005*
Fungemia, n (%)	116	10 (47.6)	48 (50.5)	0.809
CD4+ count (cells/mm^3), median (min, max)	115	29 (1, 222)	19 (2, 371)	0.175
Amphotericin B dose (mg/kg/day), mean ± SD	115	0.89±0.15	0.87±0.14	0.536
Amphotericin B duration (day), median (min, max)	116	20 (14, 80)	14 (1, 226)	0.001*
Pre-treatment CSF parameters				
Opening pressure (cmH_2O), median (min, max)	112	26 (12, 60)	26 (3, 60)	0.359
Closing pressure (cmH_2O), median (min, max)	100	16 (2, 42)	12 (1, 40)	0.218
Protein (mg/dL), median (min, max)	112	62 (29, 251)	64 (16, 580)	0.843
Sugar (mg/dL), median (min, max)	112	31 (5, 55)	43 (1, 76)	0.071
WBC (cells/mm^3), median (min, max)	113	2 (1, 6,240)	6 (1, 2,460)	0.698
End of induction (14 days) CSF parameters				
Opening pressure (cmH_2O), median (min, max)	38	25 (3, 40)	16 (3, 30)	0.318
Closing pressure (cmH_2O), median (min, max)	36	9 (5, 19)	11 (3, 19)	0.861
Protein (mg/dL), median (min, max)	47	48 (38, 203)	66 (17, 536)	0.744
Sugar (mg/dL), median (min, max)	47	41 (7, 73)	45 (5, 82)	0.297
WBC (cells/mm^3), median (min, max)	47	9 (1, 77)	9 (1, 177)	0.464

Table 7. Factors associated with 6-month survival in patients with HIV-associated cryptococcal meningoencephalitis

		6-month survival		
	Evaluable subject total = 116	Yes n = 78	No n = 38	p-value
Age (year), mean ± SD	116	38±9	39±10	0.554
Female, n (%)	116	27 (34.6)	15 (39.5)	0.609
Fungemia, n (%)	116	37 (47.4)	21 (55.3)	0.429
CD4+ count (cells/mm^3), median (min, max)	115	24 (1, 222)	21 (2, 371)	0.936
Amphotericin B dose (mg/kg/day), mean ± SD	115	0.87±0.15	0.88±0.15	0.894
Amphotericin B duration (day), median (min, max)	116	14 (10, 226)	13 (1, 49)	0.007*
Pre-treatment CSF parameters				
Opening pressure (cmH_2O), median (min, max)	112	25 (3, 60)	29 (12, 60)	0.013*
Closing pressure (cmH_2O), median (min, max)	100	12 (1, 32)	14 (1, 42)	0.128
Protein (mg/dL), median (min, max)	112	65 (22, 377)	60 (16, 580)	0.142
Sugar (mg/dL), median (min, max)	112	41 (1, 69)	43 (5, 76)	0.758
WBC (cells/mm^3), median (min, max)	113	8 (1, 6,240)	2 (1, 2,460)	0.021*
End of induction (14 days) CSF parameters				
Opening pressure (cmH_2O), median (min, max)	38	16 (3, 40)	27 (5, 29)	0.281
Closing pressure (cmH_2O), median (min, max)	36	10 (3, 19)	13 (5, 19)	0.274
Protein (mg/dL), median (min, max)	47	59 (17, 536)	126 (29, 427)	0.208
Sugar (mg/dL), median (min, max)	47	44 (5, 82)	36 (14, 73)	0.497
WBC (cells/mm^3), median (min, max)	47	9 (1, 132)	10 (2, 177)	0.609

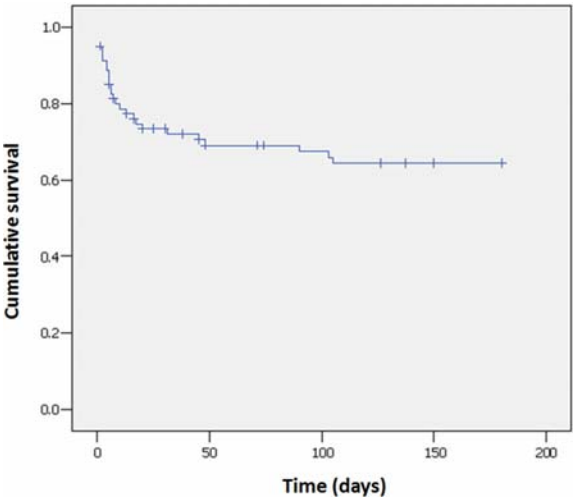

Fig. 2 Survival in patients with HIV-associated cryptococcal meningoencephalitis (n = 81).

retrospective study with a relatively small sample size. Although there is a trend of several factors that were associated with outcomes, it was not demonstrated in multivariate analysis. A larger prospective cohort study is therefore warranted to confirm these findings.

In conclusion, the present study highlights an important awareness for caring patients with cryptococcal meningitis, especially those with HIV infection. Inadequate antifungal treatment during induction is the most likely cause of unfavorable outcomes and mortality. New strategies and/or guidelines are warranted to improve survival. A cohort prospective study should be conducted to discover more accurate prognostic factors in correlation with outcomes related to treatment options.

Acknowledgement

The authors wish to thank Siriraj Research Grant for funding support and Dr. Varalak Srinonpraseet (Department of Medicine) and Dr. Sasima Tongsai (Department of Research Promotion) for their assistance in statistical analysis. We are also grateful to Ms. Sukanya Chanboonchuay and Ms. Maneerat Srichong (Division of Infectious Diseases and Tropical Medicine) for their general assistance. Dr. Methee Chayakulkeeree is supported by "Chalermphrakiat Grant", Faculty of Medicine Siriraj Hospital, Mahidol University.

Potential conflicts of interest

None.

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. Epidemiological Information Section, Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health of Thailand. [Online] Available from: http://www.boe.moph.go.th/files/report/20110401_45027790.pdf [Accessed 15th December 2013].
3. Dromer F, Mathoulin-Pelissier S, Fontanet A, Ronin O, Dupont B, Lortholary O. Epidemiology of HIV-associated cryptococcosis in France (1985-2001): comparison of the pre- and post-HAART eras. AIDS 2004; 18: 555-62.
4. Nath DS, Kandaswamy R, Gruessner R, Sutherland DE, Dunn DL, Humar A. Fungal infections in transplant recipients receiving alemtuzumab. Transplant Proc 2005; 37: 934-6.
5. Islam S, Das A, Islam N. Cryptococcosis in organ transplantation. Mymensingh Med J 2010; 19: 142-3.
6. Chayakulkeeree M, Perfect JR. Cryptococcosis. Infect Dis Clin North Am 2006; 20: 507-44, v-vi.
7. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis 2010; 50: 291-322.
8. Imwidthaya P, Kuvanont S. Two-year experience with Cryptococcus neoformans in Siriaj Hospital. Siriraj Med J 1992; 44: 216-8.
9. Imwidthaya P, Sethakorn C, Chaiprasert A, Sutthent R, Poung-varin N. Cryptococcus neoformans in Siriraj Hospital 1994-1995. Siriraj Med J. 1997; 49: 1145-52.
10. Kiertiburanakul S, Wirojtananugoon S, Pracharktam R, Sungkanuparph S. Cryptococcosis in human immunodeficiency virus-negative patients. Int J Infect Dis 2006; 10: 72-8.
11. Wachirutmanggur L, Prayoonwiwat N, Poung-varin N, Viriyavejakul A. The Comparative Study of CSF Findings in AIDS and Non-AIDS Patients with Cryptococcal Meningitis. Siriraj Med J 1994; 46: 447-51.
12. Lee YC, Wang JT, Sun HY, Chen YC. Comparisons of clinical features and mortality of cryptococcal meningitis between patients with and without human immunodeficiency virus infection. J Microbiol Immunol Infect 2011; 44: 338-45.
13. Majumder S, Mandal SK, Bandyopadhyay D. Prognostic markers in AIDS-related cryptococcal meningitis. J Assoc Physicians India 2011; 59: 152-4.
14. Lessells RJ, Mutevedzi PC, Heller T, Newell ML. Poor long-term outcomes for cryptococcal meningitis in rural South Africa. S Afr Med J 2011; 101: 251-2.
15. Bennett JE, Dismukes WE, Duma RJ, Medoff G, Sande MA, Gallis H, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptoccal meningitis. N Engl J Med 1979; 301: 126-31.
16. 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.
17. Dromer F, Bernede-Bauduin C, Guillemot D, Lortholary O. Major role for amphotericin B-flucytosine combination in severe cryptococcosis. PLoS One 2008; 3: e2870.
18. 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.

ลักษณะทางคลินิกและผลการรักษาผู้ป่วยเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอคคัสในสถานที่ทรัพยากรจำกัด

เมธี ชยะกุลดีรี, ภัทรภร วังจินดา

ภูมิหลัง: *โรคติดเชื้อราคริปโตคอคคัสเป็นโรคติดเชื้อฉวยโอกาสที่มีอันตรายถึงชีวิตโดยเฉพาะในผู้ป่วยติดเชื้อเอชไอวี อัตราการตายของผู้ป่วยเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอคคัสในคนไทยสูงมาก การศึกษาปัจจัยที่สัมพันธ์กับการรักษาที่ล้มเหลว มีความสำคัญเพื่อนำมาปรับปรุงให้ผลการรักษาดีขึ้น*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาย้อนหลังจากเวชระเบียนผู้ป่วยที่ติดเชื้อราคริปโตคอคคัสในโรงพยาบาลศิริราช ระหว่างปี พ.ศ. 2548 ถึง พ.ศ. 2551 โดยวิเคราะห์ถึงการรักษา ผลการรักษา อัตราการรอดชีวิต อัตราการตายและปัจจัยที่มีผลต่อผลการรักษา*

ผลการรักษา: *มีผู้ป่วยในการศึกษาทั้งหมด 143 ราย อายุเฉลี่ย 39 ปีและเป็นเพศชายร้อยละ 58.7 ผู้ป่วย 124 ราย (ร้อยละ 86.7) ติดเชื้อเอชไอวีร่วมด้วย และในจำนวนนี้มีผู้ป่วยเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอคคัส 116 ราย ผู้ป่วยเอชไอวีที่มีเยื่อหุ้มสมองอักเสบมีผลการรักษาที่ดีร้อยละ 55.2 และ อัตรารอดชีวิตที่ 6 เดือน ร้อยละ 67.2 พบมีการกลับเป็นซ้ำในผู้ป่วย 21 ราย (ร้อยละ 18.1) ปัจจัยที่สัมพันธ์กับการตอบสนองดีทางคลินิกคือ ความดันน้ำไขสันหลังขณะเปิดและปิดต่ำและจำนวนเม็ดเลือดขาวในน้ำไขสันหลังสูง ผู้ป่วยร้อยละ 56.8 มีการตอบสนองทางจุลชีววิทยาที่ดีและปัจจัยที่สัมพันธ์กับการตอบสนองที่ดีดังกล่าว คือ ปริมาณเม็ดเลือดขาวซีดี 4 ที่ต่ำกว่าและการได้รับยาแอมโฟเทอริซินบีที่นานกว่า ค่ามัธยฐานของระยะเวลาที่น้ำไขสันหลังปลอดเชื้อหลังการรักษา คือ 30 วัน ปัจจัยที่มีผลต่อการรอดชีวิตคือการได้ยาแอมโฟเทอริซินบีที่นานกว่า ความดันน้ำไขสันหลังขณะเปิดต่ำกว่าและเม็ดเลือดขาวในน้ำไขสันหลังที่สูงกว่า*

สรุป: *ผู้ป่วยเอชไอวีที่มีเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอคคัสมีอัตราการตายสูงและสัมพันธ์กับการได้รับการรักษาระยะแรกไม่เพียงพอ ทำให้ไม่สามารถทำให้น้ำไขสันหลังปลอดเชื้อได้ ควรมีการศึกษาและแนวทางการรักษาใหม่ในที่ที่มีทรัพยากรจำกัดเพื่อเพิ่มอัตราการรอดชีวิต*