Management of cryptococcal meningitis in HIV-infected patients: Experience from western India

Atul K. Patel, Ketan K. Patel, Rajiv Ranjan, Shalin Shah, Jagdish K. Patel
Infectious Diseases Consultant, Infectious Diseases Clinic, Adit Molecular Diagnostics, “Vedanta” Institute of Medical Sciences, Navarangpura, Ahmedabad - 380 009, Neurology Department, Sterling Hospital, Memnagar, Ahmedabad - 380 052, India

Abstract

Introduction: Cryptococcal meningitis is one of the acquired immunodeficiency syndrome defining infections with high mortality. Amphotericin B is the preferred drug for induction therapy. Despite advances in human immunodeficiency virus (HIV) treatment, Antiretroviral Treatment (ART) roll-out programs and availability of amphotericin B, cryptococcal meningitis remains an important cause of mortality in the African and other developing countries. Materials and Methods: We carried out a prospective observational study to determine the treatment response rate, tolerability and outcome of patients with cryptococcal meningitis in HIV treated with amphotericin B. Descriptive statistic was used to analyze the data. Results: A total of 27 patients were diagnosed with cryptococcal meningitis during the study period. Headache (96.29%) was the single most common presenting symptom of cryptococcal meningitis in HIV-infected patients, followed by vomiting (77.77%) and fever (66.66%). Cerebrospinal fluid (CSF) routine and microscopic examination was within normal limits in six patients. CSF became sterile on the 12th day of Amphotericin B in 55.55% of the patients while 33.33% had positive CSF cultures. Patients were started with ART after achieving sterile CSF and tolerated at least 2 weeks of fluconazole consolidation treatment and were free from symptoms. Median time for antiretroviral treatment initiation was 35 (14–90) days after completion of Amphotericin B treatment. One patient developed immune reconstitution inflammatory syndrome (IRIS) after ART. Conclusions: We found that the recommended 2 weeks induction treatment with Amphotericin B monotherapy for HIV patients with cryptococcal meningitis in resource-limited settings may be suboptimal for at least one-third of the patients. Extending the therapy to 3 weeks is likely to result in sterilization of the CSF in a majority of these patients. This finding requires confirmation by a larger sample size in appropriately powered studies. Delaying ART initiation by at least 2 weeks after amphotericin B treatment may decrease the incidence of IRIS.

Key words: Amphotericin B, cryptococcal meningitis, HIV

INTRODUCTION

Cryptococcal meningitis is one of the acquired immunodeficiency syndrome-defining infections. Although opportunistic infections are declining after the availability of antiretroviral treatment in developing countries, many patients are diagnosed with cryptococcal meningitis due to late presentation.[9] Cryptococcus is a ubiquitous environmental fungus in many parts of the world. This opportunistic fungal infection usually produces infection in immunocompromised hosts like human immunodeficiency virus (HIV) subjects, diabetics, solid organ transplant recipients and patients receiving immunosuppressive treatment. Headache may be the only symptom as presenting
feature of cryptococcal meningitis in HIV. It is crucial to understand that, in HIV-infected patients, cryptococcal meningitis can be present even in the absence of fever and meningismus. More than 75% of the patients with cryptococcal meningitis in HIV-infected patients have fever, most also have headache, but a substantial number do not have these manifestations. Some patients may present with isolated obtundation, cranial neuropathies, cognitive dysfunction or seizures.[2,3] Cryptococcal meningitis can have a very indolent, subacute presentation in HIV-infected patients, requiring a high index of suspicion. Diagnosis is performed by cerebrospinal fluid (CSF) examination with India Ink preparation, cryptococcal antigen test (CrAg) in CSF/serum and CSF culture. Neuroimaging also helps in diagnosing associated complications of cryptococcal meningitis, like cryptococcomas, infarcts, hydrocephalus, etc. Amphotericin B is the drug of choice as induction therapy. Despite advances in HIV treatment, ART roll-out programs and availability of Amphotericin B, cryptococcal meningitis remains an important cause of mortality in the African and other developing countries.[4-6]

MATERIALS AND METHODS

We carried out a prospective observational study to determine the treatment response rate, tolerability and outcome of patients with cryptococcal meningitis in HIV patients treated with amphotericin B. HIV patients attending the clinic between December 2006 and January 2010 and diagnosed with cryptococcal meningitis were prospectively followed-up, especially with regard to clinical presentation, CD4 count, CSF abnormalities, response to treatment, time to start ART and any IRIS. Data were recorded in Microsoft Excel sheets by the treating physicians at the Infectious Diseases Clinic.

Diagnosis

Suspected patients underwent CSF examination, India ink preparation, CSF CrAg and CSF culture. Patients with CSF cryptococcal antigen positivity with or without India Ink positivity were treated. Patients presenting in altered sensorium with a focal neurological deficit or intense headache not improving despite a lumbar tap were subjected to neuroimaging.

Treatment

All patients were hospitalized and a central line was placed. Conventional Amphotericin B 0.7 mg/kg/day (Amphotericin B deoxycholate) was used as induction therapy. Amphotericin B was infused in 5% dextrose over 8 h and the patients received 500 ml of 0.9% Normal saline (NS) before infusion to reduce Amphotericin B-related toxicity. In addition to this, patients were encouraged to ensure liberal intake of fluids and coconut water, citrus fruits and banana daily. Amphotericin toxicity was monitored with twice-weekly creatinine and K level. Patients with hypokalemia and requiring K supplementation were tested daily. These patients’ calcium and magnesium levels were also checked and corrected if required. Amphotericin B infusion was discontinued in patients with rising creatinine levels and resumed once creatinine levels touched baseline. Fever and chills related to Amphotericin B infusion were treated with inj hydrocortisone 50 mg IV sos. Raised intracranial pressure (ICP) was controlled with lumbar tap and mannitol. Frequency of lumbar tap was guided by patient’s clinical symptoms. Fifteen to 20 ml of CSF was removed at one time to control the raised ICP.

Successful response

Treatment response was defined as sterile CSF culture at day 12. Patients with persisting positive CSF cultures were continued on Amphotericin B infusion for one more week and evaluated with repeat CSF culture. They were then consolidated with 400 mg of fluconazole for 8 weeks and maintained on fluconazole 200 mg/day.

Patients were followed-up for a minimum of 3 months after diagnosis of cryptococcal meningitis. Descriptive statistics were used to analyze the data.

RESULTS

A total of 27 patients were diagnosed with cryptococcal meningitis during the study period. Baseline characteristics of these patients are described in Table 1.

Headache (96.29%) was the single most common presenting symptom of cryptococcal meningitis in HIV-infected patients, followed by vomiting (77.77%) and fever (66.66%). Cryptococcal meningitis was the first presenting illness in 22 (78.57%) patients, while six (21.43%) patients developed cryptococcal meningitis on ART. Of these, three had unmasking of cryptococcal meningitis and three patients defaulted ART with clinical failure. Two patients had two episodes of cryptococcal meningitis, having defaulted ART and responded both times to the same regimen.

CSF routine and microscopic examination was within normal limits in six patients, while 20 had elevated proteins, six patients’ CSF sugar was <50% of blood sugar and the CSF white blood cell (WBC) count was >5 in 13 patients.
Magnetic resonance imaging (MRI) of the brain was performed in 11 patients. MRI abnormalities included cerebral atrophy, left parietal irregular hyperintense lesion, cerebritis with meningeal inflammation, white matter lesion, cryptococcoma and cranial venous sinus thrombosis in one patient each, while it was normal in five patients.

Adverse drug reactions to Amphotericin B were generally mild and patients tolerated the drug well. Six patients developed renal dysfunction (defined as any degree of elevation of serum creatinine), which improved after drug discontinuation. These patients safely completed the prescribed course of Amphotericin B treatment. One patient developed IRIS after ART. Symptoms of IRIS were fever, headache and lymph node TB IRIS.

**DISCUSSION**

Cryptococcal disease remains an important presenting illness in HIV-infected patients in India. We describe a prospective series of cryptococcal meningitis in HIV patients at a tertiary referral center in Gujarat. Headache, vomiting and fever were three important presenting symptoms of cryptococcal meningitis in our series. CSF findings in our series, in contrast to the Kumar et al. study, were normal in six (21.43%) subjects, whereas they showed elevated proteins in 71.43% vs. 45% in the Kumar et al. study, CSF sugar was low in 21.43% vs. 75% in the Kumar et al. study and CSF WBC count was >5 in 13 (46.43%) patients with 100% lymphocytic predominance as against 55% in Kumar’s study. CSF India Ink examination was positive in 96.29% vs. 85% in the Kumar et al. study while CrAg was positive in all patients in both studies. We had a 100% culture positivity vs. 90% in the Kumar et al. study.

Treatment with flucytosine plus Amphotericin B is recommended in many reference books and guidelines. The addition of flucytosine results in faster sterilization of the CSF and fewer relapses than with the use of Amphotericin B alone, but there is no difference in mortality at the 14th day between the two regimes. However, for patients receiving antiretroviral therapy, the relapse-reduction advantage from adding flucytosine is likely to be very small.

In the present series, Amphotericin B monotherapy was effective in sterilizing CSF at the 12th day in 55.55% of the patients; one patient received 3rd week of Amphotericin B with 5 flucytosine 100 mg/kg/day while two (7.40%) patients had scanty growth at day 5 and had been started on fluconazole consolidation regimen. Three patients (11.11%) were lost to follow-up (due to financial constraints, they opted for treatment at their native place and did not present for follow-up) and one patient (cryptococcoma and meningoencephalitis) died in the hospital during treatment.

**Art**

Patients were started with ART after achieving sterile CSF and tolerated at least 2 weeks of fluconazole consolidation treatment and were free from symptoms. Median time for antiretroviral treatment initiation was 35 (14–90) days after completion of Amphotericin B treatment. One patient developed IRIS after ART. Symptoms of IRIS were fever, headache and lymph node TB IRIS.

---

**Table 1: Baseline characteristics of the patients**

| Parameters                  | Results (n = 27) |
|-----------------------------|-----------------|
| Age in years, median (range)| 37 (26–45)      |
| Sex:                        |                 |
| Male                        | 23 (85.19%)     |
| Female                      | 4 (14.81%)      |
| Weight (kg)                 | 50 (30–70)      |
| Serum creatinine            | 0.82 (0.82–1.53)|
| CD4 count                   | 73 (8–193)      |
| Symptoms:                   |                 |
| Headache                    | 26 (96.29%)     |
| Seizure                     | 9 (33.33%)      |
| Altered sensorium           | 9 (33.33%)      |
| Focal neurological deficit  | 4 (14.81%)      |
| Fever                       | 18 (66.66%)     |
| Vomiting                    | 21 (77.77%)     |
| Dizziness                   | 10 (37.03%)     |
| Associated OIs:             |                 |
| TB                           | 6 (22.22%)      |
| Candida                     | 14 (51.85%)     |
| Diarrhea                    | 3 (11.11%)      |
| PCP                          | 1 (3.70%)       |
| CSF abnormalities            |                 |
| Protein                     | 90 (26–360)     |
| Sugar                       | 44 (13–83)      |
| Cells                       | 5 (1–180)       |
| India Ink                   | 26 (96.29%)     |
| Cryptococcal antigen titer  | 8 (2–16)        |
| Culture at baseline         | 27 (100%)       |

---

*Patel, et al.: Management of cryptococcal meningitis*
consolidation and were continued the same till they were asymptomatic. Six (22.22%) patients received 3 weeks of Amphotericin B to sterilize CSF. All patients received fluconazole 400 mg for 8 weeks as consolidation followed by 200 mg daily as maintenance therapy.

CSF sterilization is the goal of therapy for cryptococcal infection. However, it is common for HIV-infected patients to have positive cultures at the end of induction therapy. In one study, 40% of the patients completing induction therapy with Amphotericin B plus flucytosine and 28% of those completing consolidation therapy with fluconazole had positive CSF cultures. In our series, 55.55% of the patients achieved sterile CSF at the 12th day of Amphotericin B monotherapy. 25.93% patients required 3 weeks of Amphotericin B treatment to achieve sterile CSF. This finding suggests that patients should be subjected for CSF culture before discontinuing Amphotericin B as induction therapy. Persistent cryptococcal infection might lead to IRIS following ART initiation. Untreated cryptococcal meningitis is universally fatal. Studies from African countries have reported a very high mortality, while the morbidity and mortality in HIV patients with cryptococcal meningitis in developed countries is 2.5–15%. Common explanation given in various studies include late presentation with low CD4 counts, Amphotericin B toxicity, uncontrolled raised ICP, focal neurologic deficit and IRIS. A high mortality rate of 33.87% at week 4 was observed in Kwa Zulu Natal by Lightowler. In another study, the mortality was 14% at 2 weeks and 22% at 10 weeks. A study from Thailand showed a 16% mortality at 2 weeks and 24% at 4 weeks. While the Kumar et al. study from north India reported a 7.5% mortality, in the present series, it was 3.57%, which compares well with the series reported from the developed countries. An established aggressive format of management of patients with cryptococcal meningitis at our tertiary care center under expert supervision, which includes a central line placement, adequate pre-hydration and prolonged Amphotericin B infusion to reduce drug-related toxicity, avoiding concomitant nephrotoxic drugs, control of raised ICP by therapeutic lumber tap as and when required and reducing the chances of IRIS by delaying the commencement of ART by 2 weeks after achievement of a sterile CSF, probably resulted in reduced mortality in our study as compared to that of other studies. It has been well studied that continuous slow infusion of Amphotericin B and pre-hydration is associated with lesser toxicity and a better outcome.

The rehospitalization rate is also high in some of the studies. We had to readmit three (11.11%) patients, two with neurological deterioration and one with hypokalemia. The reported incidence of IRIS in patients treated for cryptococcal meningitis varies by geographic region, and ranges between 4.2 cases and 18.2 cases per 100 person-years of follow-up. The results of a recent prospective study showed a higher incidence of cryptococcus-associated IRIS at 47 cases per 100 person-years of follow-up (95% confidence interval [CI]: 25–80). The variability in incidence is related, to some degree, to the differences in the definitions of IRIS, the burden of disease and the intensity of follow-up. Studies from developing countries favor a delay of 10 weeks after initiation of treatment for starting ART. In our series, the incidence of IRIS was low (3.7%), probably due to the delay in initiation of ART by at least after 2 weeks after attainment of a sterile CSF.

**CONCLUSIONS**

We found that the recommended 2-week induction treatment with Amphotericin B monotherapy for HIV patients with cryptococcal meningitis in resource-limited settings may be suboptimal for at least one-third of the patients. Extending the therapy to 3 weeks is likely to result in sterilization of the CSF in a majority of these patients. This finding requires confirmation by a larger sample size in appropriately powered studies. Delaying ART initiation by at least 2 weeks after Amphotericin B treatment may decrease the incidence of IRIS.

**REFERENCES**

1. Pappas PG. Cryptococcosis in the developing world: An elephant in the parlor. Clin Infect Dis 2010;50:345-6.
2. Rozenbaum R, Goncalves AJ. Clinical epidemiological study of 171 cases of cryptococcosis. Clin Infect Dis 1994;18:369-80.
3. Jarvis JN, Harrison TS. HIV-associated cryptococcal meningitis. AIDS 2007;21:2119-29.
4. Sloan D, Dlamini S, Dedicoat M. Management of cryptococcal meningitis in resource-limited settings: A systematic review. S Afr Med J 2009;99:310-2.
5. Sloan D, Dlamini S, Paul N, Dedicoat M. Treatment of acute cryptococcal meningitis in HIV infected adults, with an emphasis on resource-limited settings. Cochrane Database Syst Rev 2008;CD005647.
6. Sloan DJ, Dedicoat MJ, Laloo DG. Treatment of cryptococcal meningitis in resource limited settings. Curr Opin Infect Dis 2009;22:455-63.
7. 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.
8. Perfect JR, Dismukes WE, Droemer 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.
9. Stamm AM, Diasio RB, Dismukes WE, Shadomy S, Cloud GA, Bowles CA, et al. Toxicity of amphotericin B plus flucytosine in 194 patients with cryptococcal meningitis. Am J Med 1987;83:236-42.
10. 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.
11. Chuck SI, Sande MA. Infections with Cryptococcus neoformans in the acquired immunodeficiency syndrome. N Engl J Med 1989;321:794-9.
12. Jarvis JN, Meintjes G, Harrison TS. Outcomes of cryptococcal meningitis in antiretroviral naive and experienced patients in South Africa. J Infect 2010;60:496-8.
13. Steele KT, Thakur R, Nthobatsang R, Steenhoff AP, Bisson GP. In-hospital mortality of HIV-infected cryptococcal meningitis patients with C. gattii and infection in Gaborone, Botswana. Med Mycol 2010.
14. Lightowler JV, Cooke GS, Mutevedzi P, Lessells RJ, Newell ML, Dedicoat M. Treatment of cryptococcal meningitis in KwaZulu-Natal, South Africa. PLoS One 2010;5:e8630.
15. 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.
16. 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;45:226-33.
17. Kumar S, Wanchu A, Chakrabarti A, Sharma A, Bambery P, Singh S. Cryptococcal meningitis in HIV infected: Experience from a North Indian tertiary center. Neurol India 2008;56:444-9.
18. Falci DR, Lunardi JW, Ramos CG, Bay MB, Aquino VB, Goldani LZ. Continuous infusion of amphotericin B deoxycholate in the treatment of cryptococcal meningoencephalitis: Analysis of safety and fungicidal activity. Clin Infect Dis 2010;50:e26-9.
19. Lortholary O, Fontanet A, Memain N, Martin A, Sitbon K, Dromer F. Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococciosis in France. AIDS 2005;19:1043-9.
20. Lawn SD, Bekker LG, Myer L, Orrell C, Wood R. Cryptococcosis in HIV. AIDS 2005;19:2050-2.
21. Shelburne SA 3rd, Darcourt J, White AC Jr, Greenberg SB, Hamill RJ, Atmar RL, et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. Clin Infect Dis 2005;40:1049-52.
22. Sungkanuparph S, Filler SG, Chetchotisakd P, Pappas PG, Nolen TL, Manosuthi W, et al. Cryptococcal immune reconstitution inflammatory syndrome after antiretroviral therapy in AIDS patients with cryptococcal meningitis: A prospective multicenter study. Clin Infect Dis 2009;49:931-4.
23. Makadzange AT, Ndlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-Saharan Africa. Clin Infect Dis 2010;50:1528-8.
24. Manosuthi W, Chottanapund S, Sungkanuparph S. Mortality rate of early versus deferred initiation of antiretroviral therapy in HIV-1-infected patients with cryptococcal meningitis. J Acquir Immune Defic Syndr 2008;48:508-9.

Source of Support: Nil. Conflict of Interest: None declared.