POSTER 842

Timing of Immune Reconstitution Cryptococcosis after Antiretroviral Therapy in HIV-infected Patients with Cryptococcal Meningitis

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BACKGROUND

Cryptococcosis is the most common lethal fungal infection in AIDS patients. The introduction of combined antiretroviral therapy (ART) has markedly decreased the rates of opportunistic infections, the progression to AIDS, and the overall mortality for HIV-infected patients. After initiation of ART, some patients experience immune reconstitution inflammatory syndrome (IRIS), a well recognized complication of ART in patients with very low initial CD4 cell counts. This syndrome has been described in multiple opportunistic pathogens commonly with *Mycobacterium avium* complex, *Mycobacterium tuberculosis*, *Cryptococcus neoformans,* cytomegalovirus and hepatitis virus. Various studies reported that 8-50% of patients with cryptococcal infection who responded to ART developed cryptococcal IRIS despite the use of fluconazole therapy. In non-cryptococcal IRIS, most patients present in the first 8 weeks following the start of ART. However, there is little information regarding timing of cryptococcal IRIS.

METHODS

To clarify the timing of cryptococcal IRIS after ART in AIDS patients, a retrospective cohort study was conducted among HIV-infected patients who were initiated ART after the first episode of culture-proved cryptococcal meningitis. Cryptococcal IRIS was defined as culture-negative cryptococcosis after immunological response to ART according to the criteria previously described. Kaplan-Meier survival analysis was used to determine the timing of cryptococcal IRIS occurrence after ART. Cox proportional hazard model was used to determine the predicting factor of cryptococcal IRIS.

RESULTS

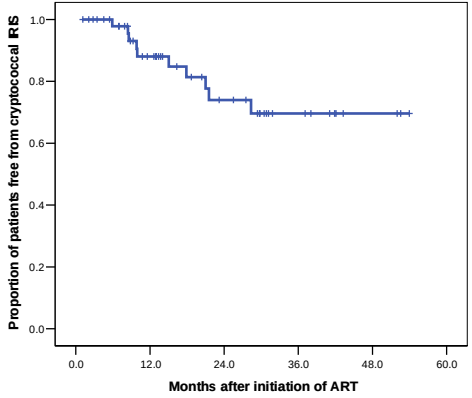
There were 52 patients with a mean age of 34.4 years and 60% were males. Baseline characteristics and treatment outcomes of ART are shown in Table 1. During a median (range) follow-up period of 15.7 (7.9-54.0) months, 10 patients (19%) developed cryptococcal IRIS at a timing of 3.0-27.3 months after initiation of ART. All patients presented with aseptic meningitis: high opening pressure, positive cryptococcal antigen in CSF, and culture-negative. ART was continued in all patients and no patient with cryptococcal IRIS died.

From Kaplan-Meier analysis, the median survival (free from cryptococcal IRIS) duration was >54 months. The 75% survival (free from cryptococcal IRIS) duration was 21.5 months (Figure 1). Among patients with cryptococcal IRIS, the median time to develop this syndrome was 9.9 (95% confidence interval, 3.9-17.9) months. The cumulative 25% and 75% occurrence of cryptococcal IRIS were at 8.6 and 21.0 months, respectively. From Cox proportional hazard model including various factors (baseline CD4, baseline HIV RNA, fungemia at baseline, cryptococcal antigen titer, type of ART regimen, initiation of ART within 2 months of cryptococcosis, CD4 and HIV RNA change at 6 and 12 months after ART), there were no factors to predict the occurrence or timing of cryptococcal IRIS.

Table 1. Baseline characteristics of 52 patients

Characteristics	Value (n=52)
Male gender, number (%)	31 (60)
Age, mean (SD)	34.4 (6.9)
Median (range) CD4 cell count, cells/mm^3	26 (1-93)
Received secondary prophylaxis, number (%)	52 (100)
Median (range) time of ART initiation after diagnosis of cryptococcal meningitis, months	2.6 (0.8-2.6)
ART regimen	
NNRTI-based regimen	50 (96)
PI-based regimen	2 (4)
At 6 months of ART	
Median (range) CD4 cell count, cells/mm^3	121 (59-203)
Achieve HIV RNA <50 copies/mL, number (%)	46 (88)
At 12 months of ART	
Median (range) CD4 cell count, cells/mm^3	237 (87-302)
Achieve HIV RNA <50 copies/mL, number (%)	41 (79)

Figure 1. Kaplan-Meier survival curve demonstrating timing of cryptococcal IRIS after initiation of ART



DISCUSSION

The results from the present study has demonstrated that, with a long-term follow-up period, the timing of cryptococcal IRIS appears to be quite variable. Interestingly, this syndrome is uncommon within the first three months of ART and may occur as late as 27 months after initiation of ART. IRIS presenting during the first 3 months of ART reflects an immune response against an active infection by opportunistic pathogens whereas late IRIS may result from an immune response against the antigens of nonviable pathogens. This may explain why secondary prophylaxis of cryptococcosis cannot prevent cryptococcal IRIS. Unfortunately, there was no predicting factor for timing of cryptococcal IRIS found in the present study. As mentioned above, this syndrome can occur as late as more than two years. This warrants the difficulty to diagnose cryptococcal IRIS particularly if physicians are not aware of this syndrome.

CONCLUSION

In summary, cryptococcal IRIS occurs at a rate of 19% and at a median time of 10 months after initiation of ART in advanced HIV-infected patients with cryptococcal meningitis. cryptococcosis within the first 3 months of ART is uncommon and this syndrome may occur as late as 27 months after ART. During the first 3 years of ART, immune reconstitution cryptococcosis should be recognized in patients presented with culture-negative cryptococcosis and occurrence of this syndrome should not indicate ART failure.