H-2334

Immune Reconstitution Syndrome in HIV-infected Patients with Cryptococcal Meningitis: A Prospective Study

Weerawat Manosuthi[1,2], Supeda Thongyen[1], Sukanya Chimsuntorn[1], Somnuek Sungkanuparph[2] *(Contact: idweerawat@yahoo.com)*

[1]Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, 11000 [2]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, 10400, Thailand

SUMMARY

Background: Data of rate, risk factors and outcomes of cryptococcal meningitis (CM)-related immune reconstitution syndrome (IRS) in HIV-infected patients particularly from prospective study are scanty.

Methods: A prospective study was conducted in HIV-infected patients who were diagnosed with first episode of CM during 2005-2007. All were initiated antiretroviral therapy (ART) at week 6 and were followed until 6 months after CM diagnosis. Cerebrospinal fluid (CSF) were analysed at day 0, day 14 and at IRS diagnosis. CD4 and HIV-1 RNA were assessed at baseline and 6 months.

Results: A total of 58 patients were enrolled with mean±SD age of 36±7 years and 62% male. Median (IQR) baseline CD4 was 14 (7-23) cells/mm3 and median (IQR) log HIV-1 RNA was 5.6 (5.2-5.9). Nine (16%) developed cryptococcal IRS (IRS group). Median (IQR) titer of CSF cryptococcal Ag at day 14 was 1:2048 (1:512-1:4096) in IRS group and 1:512 (1:64-1:1024) in non IRS group (P=0.019). Other baseline characteristics were not different between 2 groups (P >0.05). Median (IQR) time from ART to IRS was 2.6 (1.2-3.6) months. IRS patients developed recurrent headache with median CSF opening pressure of 460 mm H2O. Mean CSF protein at IRS increased from mean value at day 14 (102 vs 46 mg/dL, P=0.011). By multivariate analysis, patients who had CSF Ag >1:512 at day 14 were 17 times more likely to develop IRS (P=0.032, OR=16.667, 95%CI=1.264-200.000). Eight received corticosteroids and 1 was placed lumbar drainage. No patients died after occurring IRS.

Conclusions: The rate of cryptococcal IRS is 16% in HIV-infected patients with CM. Sustained CSF cryptococcal antigen at high titer after 14 days of antifungal treatment is an important risk factor for IRS. Recognition of cryptococcal IRS and proper management are crucial for the favorable treatment outcomes of cryptococcal IRIS.

INTRODUCTION

Successful suppression of HIV replications and subsequent increment of CD4 lymphocyte is observed after receiving highly active antiretroviral therapy (HAART). If immune function improves rapidly following the initiation of ART, systemic or local inflammatory reactions at the site of the preexisting infection or unrecognized OIs may develop. This phenomenon has been termed "immune reconstitution syndrome (IRS)". Herein, we study the clinical data of cryptococcal meningitis (CM)-related IRS in HIV-infected patients from a resource-constrained setting in a prospective fashion.

Primary objective: To determine the prevalence of CM-related IRS in HIV-infected patients.

Secondary objective: To define the possible risk factors and outcomes of CM-related IRS.

METHODS

A prospective cohort study was conducted in all HIV-infected patients diagnosed with first episode of CM between 2005 and 2007 in Bamrasnaradura Infectious Diseases Institute.

Inclusion criteria were as follows:

1. HIV-infected patients >15 years of age
2. Diagnosed with the first episode of cryptococcal meningitis by positive culture
3. Naïve to antiretroviral treatment

All were initiated efavirenz-based or nevirapine-based HAART at week 6 and were followed through 6 months after CM diagnosis. CSF were analysed at day 0, day 14 and at IRS diagnosis. Blood culture for fungus was performed at day 0 and day 7. CD4 and HIV-1 RNA were assessed at day 0 and 6 months after diagnosis of cryptococcal meningitis.

RESULTS

Table 1. Characteristics at baseline and day 14 between IRS vs non-IRS

Characteristics	IRS group n = 9	Non-IRS group n = 49	*P* value
Parameters at baseline			
Age, years, median (IQR)	34.1 ± 4.0	36.0 ± 7.7	0.501
Gender: Male	6 (66.7%)	30 (61.2%)	1.000
Weight, kgs, mean±SD	47.6 ± 5.6	51.3 ± 9.7	0.268
Baseline CD4 count, cell/mm^3, mean±SD	16 ± 19	21 ± 22	0.498
Baseline % CD4 , median (IQR)	4 ± 4	4 ± 4	0.842
Baseline plasma HIV RNA, copies/ml, median (IQR)	316000 (107450-657000)	379000 (175750-725250)	0.577
CSF opening pressure, mmHg, median (IQR)	330 (200-435)	280 (215-460)	0.889
CSF protein, mg/dl, mean±SD	70.2 ± 53.5	74.2 ± 94.8	0.904
CSF sugar, mg%, mean±SD	33.2 ± 19.1	39.6 ± 21.9	0.416
CSF WBC, cells/mm^3, mean±SD	44 ± 99	53 ± 118	0.827
CSF cryptococcal antigen titer, median (IQR)	1:4096 (1:2560-1:9096)	1:1024 (1:384-1:4096)	0.023
Serum creatinine, mg/dl, mean±SD	0.7 ± 0.3	1.1 ± 1.6	0.562
Serum alkaline phosphatase, mg/dl, mean±SD	69.6 ± 13.3	105.5 ± 66.3	0.114
Serum sodium , mmol/L, mean±SD	132.6 ± 4.9	131.1 ± 16.0	0.775
Serum AST, U/L, mean±SD	30.4 ± 15.7	41.4 ± 25.7	0.221
Total bilirubin, mg/dl, mean±SD	0.51 ± 0.19	0.67 ± 0.71	0.500
Blood culture for fungus at day 0: positive	8 of 8 (100.0%)	25 of 42 (59.5%)	0.039
Blood culture for fungus at day 7: positive	1 of 8 (12.5%)	3 of 40 (7.5%)	0.072
Parameters at day 14	n = 9	n = 39	
CSF opening pressure, mmHg, median (IQR)	280 (175-403)	240 (140-300)	0.245
CSF protein, mg/dl, mean±SD	45.7 ± 14.3	81.4 ± 112.7	0.351
CSF sugar, mg%, mean±SD	31.0 ± 10.4	41.2 ± 22.5	0.189
CSF WBC, cells/mm3, mean±SD	10 ± 7	43 ± 169	0.507
CSF cryptococcal antigen titer, median (IQR)	1:2048 (1:512-1:4096)	1:512 (1:64-1:1024)	0.019
CSF fungal culture: positve	1 (11.1%)	17 (43.6%)	0.125

A total of 58 patients were enrolled with mean±SD age of 36±±7 years and 62% male. Median (IQR) baseline CD4 was 14 (7-23) cells/mm3 and median (IQR) log HIV-1 RNA was 5.6 (5.2-5.9). All but one were positve for fungal culture. Nine (16%) patients developed cryptococcal IRS (IRS group). Table 1 compared clinical characteristics at baseline and at day 14 between IRS group and non-IRS group. Median (IQR) titer of CSF cryptococcal Ag at day 14 was 1:2048 (1:512-1:4096) in IRS group and 1:512 (1:64-1:1024) in non IRS group (P=0.019).

Median (IQR) time from ART to IRS was 2.6 (1.2-3.6) months. IRS patients developed recurrent headache with median CSF opening pressure of 460 mm H_2O. Mean CSF protein at IRS increased from mean value at day 14 (102 vs 46 mg/dL, P=0.011). Table 2 summarized CSF profiles of 9 patients who were diagnosed with CM-related IRS at each time point. By multivariate analysis, patients who had CSF Ag >1:512 at day 14 were 17 times more likely to develop IRS (P=0.032, OR=16.667, 95%CI=1.264-200.000) as shown in Table 3.

Of 58 patients, 43 (74%) survived, 13 (22%) died and 2 (3.4%) lost to follow-up after 6 months. No patients died after occurring IRS. Regarding treatment of CM-related IRS, Eight patients received corticosteroids and 1 patients was placed temporary external lumbar drainage. Eight patients needed to hospitalize. At 6 months, mean±SD CD4 cell counts were 88±54 cells/mm^3 and 122±92 cells/mm^3 in IRS and non-IRS groups, respectively (P=0.322).

CONCLUSION

The rate of cryptococcal IRS is 16% in HIV-infected patients with CM. Sustained CSF cryptococcal antigen at high titer after 14 days of antifungal treatment is an important risk factor for IRS. Recognition of cryptococcal IRS and proper management are crucial for the favorable treatment outcomes of cryptococcal IRIS.

Table 2. CSF profiles of 9 patients who were diagnosed with CM-related IRS at each time point

Risk factors	At baseline	At day 14	At time of IRS	*P* value*
CSF opening pressure, mmHg, median (IQR)	330 (200-435)	280 (175-403)	460 (250->600)	0.161
CSF protein, mg/dl, mean±SD	70.2 ± 53.5	45.7 ± 14.3	102.2 ± 50.1	0.001
CSF sugar, mg%, mean±SD	33.2 ± 19.1	31.0 ± 10.4	41.3 ± 11.4	0.020
CSF WBC, cells/mm^3, mean±SD	44 ± 99	10 ± 7	42 ± 53	0.112

* Compared values between at time of IRS diagnosis and at day 14

Table 3. Binary logistic regression of possible risk factors for CM-related IRS

Risk factors	HR	95% CI	*P* value
CSF antigen titer >1:512 at day 14	16.667	1.264-200.000	0.032
CSF protein at day 14	1.089	1.003-1.182	0.043
CSF sugar at day 14	1.093	0.981-1.217	0.106
Baseline log plasma HIV-1 RNA	1.665	0.351-7.897	0.521
Baseline CD4 cell count	1.006	0.960-1.053	0.814