Effect of cytomegalovirus viremia on mortality in patients with cryptococcal meningitis in Uganda

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Abstract

Background: Cryptococcal meningitis and tuberculosis are both major causes of death in persons with advanced HIV/AIDS. Cytomegalovirus (CMV) viremia may be associated with increased mortality in HIV-infected persons with tuberculosis. It is unknown if CMV viremia is associated with mortality in other AIDS-related opportunistic infections.

Methods: We prospectively enrolled HIV-infected Ugandans with cryptococcal meningitis from 2010-2013. Subsequently, we analyzed stored baseline samples from 111 subjects for CMV DNA. A Log Rank test and Cox Proportional Hazards model were used to consider CMV viremia association with 10-week survival.

Results: Of 111 participants, 52% (58/111) had detectable CMV DNA (median plasma viral load 281 copies/mL [IQR, 142 to 1420]). The mean age was 35 years (SD, ±8) and the median CD4⁺ T-cell count was 19 cells/µL (IQR, 9 to 70). Median CD4 counts did not differ between CMV-positive and CMV-negative (P=0.53) nor HIV viral loads (P=0.59). A total of 34 deaths occurred. The mortality was 40% (23/58) in the CMV-positive group and 21% (11/53) in the CMV-negative group by 10-weeks (Hazard Ratio=2.19; 95%CI, 1.07-4.49; P=0.033). Mortality remained significant with adjusting for factors associated with death in cryptococcal meningitis (HR=3.30; 95%CI, 1.51-7.23; P=0.003).

Conclusion: Half of persons with advanced AIDS and cryptococcal meningitis had CMV viremia. CMV viremia was significantly associated with mortality in persons with cryptococcal meningitis, even after multivariate adjustment. It remains unclear if the relatively low level CMV viremia in the setting of high baseline mortality due to cryptococcal meningitis contributes to this mortality or may reflect underlying immune dysfunction (i.e. cause vs. effect). Further investigation is warranted.

Introduction

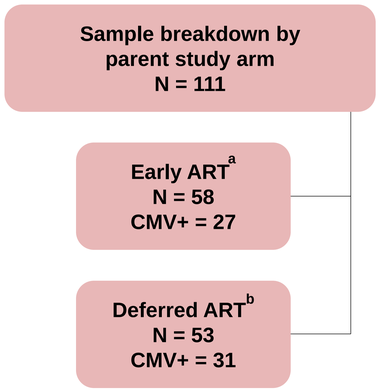
- Cryptococcal meningitis and cytomegalovirus (CMV) disease both occur in significantly immunocompromised patients, often with CD4⁺ counts < 100 cells/µL.
- CMV viremia has been associated with a 2.2-fold increased risk of developing an AIDS-defining illness, even when controlling for CD4⁺ T-cell count and plasma HIV RNA concentration.
- Meintjes et al. recently demonstrated that CMV viremia showed a trend toward increased mortality in persons with HIV-associated TB.
- No data exist on whether CMV viremia may be associated with mortality in cryptococcal meningitis. Given that CMV is treatable, such an association has potential management implications.

Methods

- Stored plasma samples were analyzed for CMV DNA concentration via RT-PCR using a lower limit-of-detection of ~75 copies/mL of plasma.
- Persons with detectable viremia were considered CMV positive versus those with no detectable viremia as CMV negative.
- Primary endpoint of this study was 10 week survival.
- Survival analysis was performed using a Log Rank test and Cox proportional hazards regression. A Kaplan Meier plot depicts time-to-event. Analysis used SPSS v.23 (IBM; Armonk, NY).

Study Population

- Analysis used samples* from the **COAT trial**: a randomized clinical trial where subjects with cryptococcal meningitis were randomized at 1 week into either an early ART or deferred ART group. The primary endpoint was 26 week survival.
- All persons received 2 weeks of amphotericin B combined with fluconazole for induction therapy, followed by standard of care antifungal consolidation and maintenance therapies.
- All persons received equivalent adjunctive therapies (e.g. therapeutic LPs, IV fluids, electrolyte replacement).
- Study enrolled patients from 2010 through 2012.



* Samples were selected randomly and by convenience. Samples represent baseline blood draw (median 6 days after diagnosis).

[a] Early ART were randomized to start ART within 48 hours of randomization at ~1 week of antifungal therapy.

[b] Deferred ART were randomized to start ART 4 – 6 weeks after meningitis diagnosis.

Baseline Characteristics

Table 1: Baseline characteristics based on CMV status

Baseline Data	CMV Negative	CMV Positive	P-Value
N per group	53 (48%)	58 (52%)	--
Deferred ART	22 (42%)	31 (53%)	0.21
Women	28 (53%)	23 (40%)	0.16
Age, years	37 [±8]	34 [±7]	0.06
CD4 count, cells/µL	18 [10-75]	20 [9-52]	0.53
HIV Viral Load, $\log_{10}$ copies/mL	5.40 [5.13–5.74]	5.45 [5.19–5.78]	0.59
CMV DNA viral load, copies/mL	--	281 [147-1350]	--
Glasgow Coma Scale <15	14 (26%)	16 (28%)	0.89
Hemoglobin, g/dL	11.4 [±2.8]	10.6 [±2.5]	0.09
CSF white cells <5 cells/µL	13 (25%)	23 (40%)	0.09

Data are N (%), mean [±SD], and median [IQR]
P-values from chi-square, t-test, or Mann-Whitney U
Abbreviations: CSF WBC, cerebrospinal fluid white blood cell count

Outcomes

Table 2: 10-week mortality by presence of CMV viremia

Outcome	CMV Negative	CMV Positive	Log-Rank P-Value
Mortality	21% (11/53)	40% (23/58)	0.028

Outcomes

Figure 1: Kaplan Meier Survival Curve by CMV status

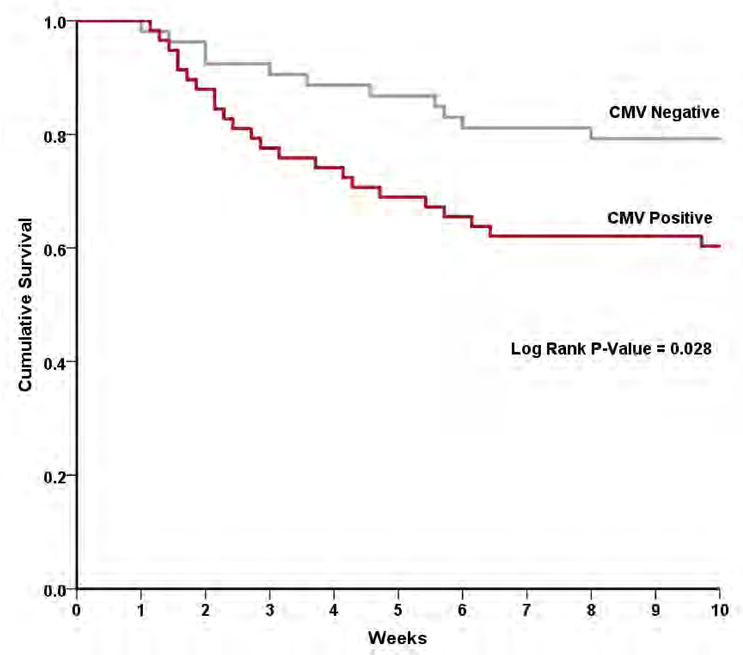


Table 3: Multivariate Cox Regression survival model

Variable	Hazard Ratio	Confidence Interval	P-Value
Women	**2.63**	**1.25 – 5.55**	**0.011**
Age, per year	1.04	0.99 – 1.09	0.145
CD4 count, per cell/µL	1.00	0.99 – 1.00	0.996
Glasgow Coma Scale <15	2.03	0.95 – 4.34	0.069
Hemoglobin, per g/dL	0.94	0.81 – 1.09	0.389
CSF WBC <5 cells/µL	0.67	0.29 – 1.51	0.332
Deferred ART	**0.39**	**0.19 – 0.81**	**0.011**
CMV Positive	**3.30**	**1.51 – 7.23**	**0.003**

Conclusions

- Persons with CMV viremia had 2-fold greater risk of death than those CMV negative in the setting of cryptococcal meningitis.
- Mortality remained significant when adjusted for other variables associated with mortality in cryptococcal meningitis.
- A randomized controlled trial is warranted to elucidate whether the presence of CMV viremia in persons with advanced HIV disease contributes to increased mortality or whether it is a marker of underlying immune dysfunction.

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