The outcome of HIV-positive late presenters according to detectable CMV DNA and anti-CMV treatment

The Outcome of HIV-positive Late Presenters According to detectable Cytomegalovirus DNA and Anti-CMV Treatment

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ABSTRACT

Background: HIV late presenters are at high risk of Citomegalovirus reactivation and end-organ disease. CMV viremia has been associated with poor survival but the effect of anti-CMV treatment has not been studied in this setting.

Methods: HIV-positive patients were included in a retrospective study if presenting with <350 CD4/uL and starting an antiretroviral treatment within 3 months of the diagnosis. Primary endpoint was 5-year survival according to the presence of CMV viremia (CMV-V), CMV end-organ disease (CMV-EOD) and anti-CMV treatment.

Results: 302 patients were included. 157 patients (52%) presented CMV-V and 44 (14.6%) CMV-EOD. 5-year mortality was higher in CMV-EOD and CMV-V patients than in CMV negative patients(11.4 vs. 9.6 vs. 0%, p=0.002). In patients with CMV viremia, 5 year-mortality was numerically higher in untreated patients (12.9% vs. 6.9%, p=0.257). At Univariate analysis the diagnosis of serious opportunistic infections (cryptococcosis, progressive multifocal leucoencephalopathy, lymphoma) (p=0.001) and the absence of a negative CMV DNA in the follow up (p<0.001) were associated with poor outcome. At multivariate analysis HCV co-infection (p=0.016, aOR 6.98, 95% CI 1.50 – 32.59), the absence of a negative CMV DNA in the follow up (p<0.001, aOR 19.40, 95% CI 3.70 – 101.64) and marginally the absence of anti-CMV treatment (p=0.052, aOR 4.944, 95% CI 0.99-24.73) were independent predictors of poor outcome.

Conclusions: CMV reactivation in HIV-positive patients with poor immunity is associated with worse prognosis: the pre-emptive use of anti-CMV therapy was associated with a better outcome in patients with CMV viremia.

BACKGROUND

Cytomegalovirus (CMV) is a betaherpesvirus that infects 60-100% adults worldwide; it establishes a latent infection after the resolution of the acute phase.[1] In immune compromised hosts the reactivation of latent virus causes a systemic disease characterized by constant or intermittent viremia and the potential to cause end-organ disease (most frequently retinitis, colitis and pneumonia). [2,3]

The clinical relevance of detecting plasma CMV-DNA in HIV-positive patients is controversial. The presence of the virus in the plasma compartment is not always associated with tissue disease [4], but also CMV-associated end-organ disease (diagnosed on biopsies or autoptic samples) have been reported in the absence of detectable viremia [5,6]. A recent study reported that CMV DNA >10086 copies/mL held a 94.1% and 95.3% specificity for retinitis and for other organ diseases, respectively [7]. Several studies found an association between CMV viremia and mortality: however it is unclear if CMV concurs to mortality or if reactivation is a proxy of a deeply compromised immune system [8,9]. Two recent studies in different settings (Thailand [10] and South Africa [11]) confirmed that CMV serum detection was associated with an increased risk of dying despite prompt highly active antiretroviral treatment (HAART) introduction.

With the introduction of HAART the role of pre-emptive anti-CMV treatment has been challenged. Upon its introduction there is a rapid increase in immune function including CMV-specific CD8+ T lymphocytes; this event might be harmful in case of immune reconstitution inflammatory syndrome (IRIS) [12]. Several data pointed out that CMV may be a leading cause of chronic immune activation and immune-senescence; the treatment of latent CMV infection with oral valganciclovir was associated, in HAART efficaciously treated patients, with a reduced prevalence of activated CD8+ T lymphocytes. [13] Chronic immuneactivation and inflammation have been reported in several organs and tissues and CMV may concur in the high prevalence of comorbidities observed in stable HIV-positive subjects. [14] Specifically a recent cohort study showed that CMV latent infection was associated with several non-HIV complications including cardiovascular and cerebrovascular diseases. [15] In addition, patients who achieved viral suppression of CMV through pre-emptive therapy with

oral ganciclovir had a significantly lower risk of developing CMV disease but not significant effect on survival. [16,17]

Given the above mentioned evidence we seek to explore the impact of treating CMV viremia in HIV-late presenters starting an antiretroviral regimen.

METHODS

A retrospective study was carried in a single Italian Institution. Patients were included if presenting with a confirmed diagnosis of HIV in the years 2000/2010, <350 CD4/uL and starting an antiretroviral treatment within 3 months of the diagnosis. Patients are routinely tested for CMV DNA even if asymptomatic. All patients included in the study had at least one follow-up visit in the following six months. Ethic Committee approval was obtained and informed consent request was waived given the retrospective nature of the study.

We collected demographic, immunological, virological, clinical and therapeutical data of the included patients. Follow up data were available for all subjects including immuno-virological results (quantitative HIV-RNA, CD4 +, CD4+ cell count and antiretroviral therapy) and clinical outcomes (defined as cure, recurrence of CMV viremia or organ disease, or death) at six months and long-term (last available visit). HIV-RNA and CMV-DNA were analysed by RT-PCR (CAP / CTM HIV-1 vs. 2.0 (CAP / CTM, Roche Molecular Systems, Branchburg, NJ and CMV MGB® Elite Kit) and CD4 + cell counts through flow cytometry.

According to the CMV status, we divided patients into three groups: CMV end-organ disease (CMV-EOD) if they had a positive CMV-DNA analysis and a diagnosed tissue localization, CMV viremia (CMV-V) if they had a positive CMV-DNA analysis from blood plasma and CMV negative if they had a CMV-DNA negative result.

Primary endpoint was 5-year survival according to the CMV status and anti-CMV treatment (5 mg/kg twice-daily gancyclovir for 2 weeks followed by 2 week once-daily administration in patients with viremia while once daily oral valganciclovir 900 mg administered according to international guidelines to patients with CMV-EOD).

Results are expressed as medians (and interquartile ranges, IQR) and the effect of different variables on survival was quantified by Log-rank test. Non-parametric tests were used for uni- and multivariate analysis. Statistical significance was considered for $p < 0.05$. Statistical analyses were performed using SPSS software (version 22.0, IBM Inc). A multivariate Cox proportional hazard model was created including CD4 cell count, CMV DNA and the presence of opportunistic infections as well as factors deemed significant at univariate analysis (Log-rank test).

RESULTS

302 patients were included, median age was 48 years (IQR 41-55) and 208 (68,9%) were males.

157 patients (52%) presented CMV viremia, 44 (14.6%) CMV end-organ disease and 101 (33,4%) where CMV negative. Baseline characteristics of patients included in the three groups are shown in table 1.

CMV-EOD patients showed lower CD4 cell count (29 vs. 51 vs. 63 cell/uL, $p<0.001$), higher HIV RNA (5.6 vs. 5.4 vs. 5.4 Log10 copies/mL, $p=0.047$) and a higher prevalence of other opportunistic infections (OIs, 70.5 vs. 65.6 vs. 46.5%, $p=0.006$) as compared to CMV-V e CMV-negative subjects. Among subjects with CMV-EOD 35 (79.5%) had a retinitis, 4 (9.1%) a gastrointestinal localization, 1 (2.3%) an encephalitis, 2 (4.5%) a retinitis and an encephalitis and 1 (2.3%) a retinitis and a myocardial localization. For one patient we have no information.

5-year mortality was higher in CMV-EOD and CMV-V patients than in CMV negative patients(11.4 vs. 9.6 vs. 0%, $p=0.002$, Log-rank analysis) as shown in Figure 1; median overall survival was 38.4 months (19.2-60.2). Beside CMV infection at Univariate analysis Hepatitis C virus (HCV) infection

(p<0.001), Progressive multifocal leukoencephalopathy (PML) (p=0.015), disseminated cryptococcosis (p<0.001) and marginally lymphoma (p=0.088) as well as these three severe opportunistic diseases (p<0.001) were associated with poor outcome. At multivariate analysis HCV co-infection (p<0.001, aOR 5.33, 95% CI 2.23- 12.75), CMV-infection (p<0.001, aOR 8.57, 95% CI 3.41-21.55) and the diagnosis of cryptococcosis/PML/lymphoma (p<0.001, aOR 3.76, 95% CI 1.81-7.79) were independent predictors of poor outcome.

Among subjects with CMV-V, 87 patients (55.4%) received anti CMV-treatment; these patients had lower CD4 cell count (39 vs. 74 cells/uL, p=0.032), higher CMV DNA (3.4 vs. 2.6 Log10 copies/mL, p<0.001) and a higher prevalence of other OIs (79.3 vs. 44.3%, p<0.001) but a lower prevalence of HCV-coinfection (12.8 vs. 28.6%, p=0.016). In patients with CMV viremia 5 year-mortality was numerically higher in untreated patients versus those that received anti-CMV medications (12.9% vs. 6.9%, p=0.257) (Fig. 2). At Univariate analysis the diagnosis of cryptococcosis/PML/lymphoma (p=0.001), the absence of a negative CMV DNA in the follow up (p<0.001) and marginally higher HIV RNA at baseline (p=0.074) and HCV infection (p=0.138) were associated with poor outcome. At multivariate analysis HCV co-infection (p=0.016, aOR 6.98, 95% CI 1.50 – 32.59), the absence of a negative CMV DNA in the follow up (p<0.001, aOR 19.40, 95% CI 3.70 – 101.64) and marginally the absence of anti-CMV treatment (p=0.052, aOR 4.944, 95% CI 0.99-24.73) were independent predictors of poor outcome.

Finally in table 2 are described the results in CD4 cell count and in HIV suppression after six and twelve months of antiretroviral therapy.

We saw no statistically significant differences in CD4 cell count or percentage increase between the three CMV groups; a small difference in CD4/CD8 ratio at 12 months favored patients with CMV-V. In the limited number of patients that had a viral load performed at 12 months, the prevalence of viral suppression was higher in CMV-neg followed by CMV-EOD and CMV-V patients.

DISCUSSION AND CONCLUSIONS

Published literature and treatment guidelines currently do not provide clear indications about a standardized approach to the treatment of CMV viremia in HIV patients. Although several recent studies suggest to treat it [7-11,15-18], other experts believe that after HAART introduction the benefits of treating CMV reactivation are futile [19]. Nevertheless treating CMV infection, even in the context of chronically treated subjects, have proven some immunological benefits [13].

Recently a French study demonstrated that, in patients with low CD4 counts, CMV viremia is a strong predictor of CMV EOD and death. Pre-emptive anti CMV treatment was associated (in un-adjusted analysis) with a lower incidence of EOD or death although in adjusted analysis CMV DNA was the only independent predictor of unfavourable outcomes; treated patients experienced severe drug-associated adverse events [19]. Our study differs from the above mentioned because we enrolled only HAART-naive patients over a longer study period (5 years) and we also included patients with CMV EOD at baseline.

In our data, CMV reactivation in HIV-positive patients with poor immunity is associated with higher mortality. Similar mortality was found in patients with CMV-V and CMV-EOD. Beside CMV infection, we observed an association with poor outcome at univariate analysis of HCV infection, PML, disseminated cryptococcosis and marginally lymphoma. At multivariate analysis HCV co-infection, CMV-infection and the diagnosis of cryptococcosis/PML/lymphoma were independent predictors of poor outcome.

If we consider patients with CMV viremia we saw better survival rates in those treated with pre-emptive anti-CMV therapy and that obtained CMV DNA undetectability. The baseline characteristics which were more frequently associated with the beginning of the anti CMV therapy were lower CD4 cell count, higher CMV DNA and a higher prevalence of other OIs but a lower prevalence of HCV-coinfection. In patients with CMV viremia 5 year-mortality was numerically higher in untreated patients versus those that received anti-CMV medications. At Univariate analysis the diagnosis of

cryptococcosis/PML/lymphoma, the absence of a negative CMV DNA in the follow up and marginally higher HIV RNA at baseline and HCV infection were associated with poor outcome. At multivariate analysis HCV co-infection, the absence of a negative CMV DNA in the follow up and marginally the absence of anti-CMV treatment were independent predictors of poor outcome.

We also observed no differences in immune reconstitution, the increase of CD4 lymphocytes was similar in viremic treated patients and not treated: the potential myelosuppression of ganciclovir has not been shown. A recent paper reported that even among individuals who started ART early (with high CD cell count), asymptomatic CMV reactivation was associated with slower CD4/CD8 recovery.[20]

Although CMV has not been reported as a significant cause of death in previous studies, we agree that CMV viremia could be associated with direct CMV pathogenic effects underestimated in their contribution to death. CMV viremia could be a cause, or a consequence, of poor immune function. However the possibility of CMV tissue replication with low plasma CMV viremia raises the doubt of undertreatment of HIV-positive advanced patients.[21]

We recognize several limitations in our study. First, the retrospective nature and the small subgroups. Between them we had low mortality in the CMV negative group and we also had some missing data regarding the treatment or the outcome of some patients and the lack of data on cause of death. We could not even retrieve information about the possible appearance of IRIS and the CMV serology for each patient. Finally, in our results, we had large confidence intervals.

In conclusion, in our restrospective analysis pre-emptive use of anti-CMV therapy was associated with a better outcome in patients with CMV viremia. This approach deserves further prospective evaluation.

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