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Study Title:	Pre-engraftment Cytomegalovirus DNAemia in allogeneic hematopoietic stem cell transplant recipients: incidence, risk factors and clinical outcomes
Request Date:	
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Background and Rationale

Cytomegalovirus DNAemia occurs frequently in allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients [1] Both high-level and persistent virus DNAemia are known risk factors for CMV end-organ disease and perhaps non-relapse mortality [2]. CMV DNAemia is usually documented after engraftment, but it may occur before. The virological features and clinical consequences of these latter early-onset episodes remain largely unexplored. The U.S. Food and Drug Administration (FDA) has recently approved letermovir for prophylaxis of CMV infection and disease in adult CMV-seropositive allo-HSCT recipients (PREVYMIS™, Merck & Co., New Jersey, USA). In accordance with the design of the phase III, double-blind trial [3] the drug may be administered as early as the day of transplant and no later than 28 days post-transplant. Nevertheless, the timing of drug inception should be contingent on the clinical impact of very early episodes of CMV DNAemia. In a recent work from our group (single-center study) [4] we found that a total 38 out of the 197 patients in our series developed CMV DNAemia before engraftment (cumulative incidence, 19%; 95% CI, 10-30.3%). Nine episodes of CMV DNAemia were detected prior to the time of donor progenitor cell infusion. A greater number of post-engraftment episodes required preemptive antiviral therapy compared with pre-engraftment episodes (62.5% vs 44.7%; *P*=0.05). The cellular content of the donor progenitor cell infusion and transplant characteristics of patients did not differ between patients with pre- or post-engraftment CMV DNAemia. The cumulative incidence of overall mortality by days 100 and 365, aGvHD by day 100 and relapse by day 365 were not significantly different between patients with pre-engraftment or post-engraftment CMV DNAemia. Our study was limited by the retrospective and single-center design and the scarce number of pre-engraftment CMV DNAemia episodes included; therefore, the results may not be extrapolated to other transplantation centers or patient cohorts. Further retrospective and prospective studies are thus required to validate the data presented herein.

References:

1. Pérez Romero P, et al. An update on the management and prevention of cytomegalovirus infection following allogeneic hematopoietic stem cell transplantation*. Future Virol* 2015; 10:113–134.

2.2.Green ML, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. *Lancet Haematol* 2016;3:e119-27.

3.3.Solano C, et al. Impact of cytomegalovirus DNAemia on overall and non-relapse mortality in allogeneic stem cell transplant recipients. *Transpl Infect Dis* 2017 Aug;19(4). E12717..

4. Solano et al., Pre-engraftment Cytomegalovirus DNAemia in allogeneic hematopoietic stem cell transplant recipients: incidence, risk factors and clinical outcomes (Bone Marrow Transplantation, 2018, in press).

Objectives

1. Assess the incidence of pre-engraftment CMV DNAemia using highly sensitive real-time PCR assays in allo-HSCT

2. Evaluate its impact of pre-engraftment CMV DNAemia on the time to engraftment, overall mortality, and non-relapse mortality.

Hypothesis

Very early episodes of CMV DNAemia have no impact on the occurrence of engraftment, overall mortality and non-relapse mortality.

Study Design/Clinical Plan

This is a multicenter, retrospective, observational and single arm study which will include all consecutive allo-HSCT recipients at risk of CMV infection allografted from 1st January 2010 until 31th December 2019 in Spanish transplant centers belonging to the "Grupo Español de trasplante hematopoyetico y terapia cellular" (GETH group). No less than 10 centers performing bot related and unrelated allo-HSCT in Spain will participate in the study.

Inclusion criteria include:

- **Recipients >18 years old**
- **CMV seropositive recipients and/or donors**
- **DNA load monitoring by real-time PCR starting from day -7 and conducted on a weekly CMV basis (0, +7, +14,…) at least until day +100**
- **First allo-HSCT**
  T-cell replete allograft

Essential variables which include patients, donor and transplant's characteristics as well as post-transplant outcome will be retrieved from MED-A of PROMISE EBMT database.

Specific CMV data (including one-year longitudinal PCR results, date of onset and type of pre-emptive antiviral therapy as well as CMV disease data) will be retrospectively reported by each participating center.

Analysis of the clinical impact of CMV DNAemia will be performed by evaluation of:

- **Time to engraftment**
- **Overall mortality**

The analysis will be performed comparing the clinical impact of CMV DNAemia as described before, in relation to time of CMV DNAemia initiation in the following groups:

- **Patients with DNAemia before engraftment vs after engrafmet**
- **Patients with DNAemia before engraftment and before HSC infusion vs patients with DNAmia before engraftment after HCS infusion**
- **Comparison of time of initiation of CMV DNAemia from day -7 to HCS infusion on a weekly basis until engraftment.**

Statistical Plans

Non-parametric and semi-parametric analyses. The probabilities of CMV DNAemia, CMV DNAemia requiring pre-emptive therapy, CMV-D, NRM and relapse will be estimated by the cumulative incidence method (marginal probability).

Competing events will be defined as follows; in the case of relapse, the competing event was NRM without the occurrence of the disease. For CMV DNAemia, CMV DNAemia requiring pre-emptive therapy, CMV-D and GVHD the competing event will be relapse or death without the event. For NRM the competing event will be relapse.

The assumption of proportional hazards over time will be tested for all explanatory covariates using a time-dependent covariate. CMV DNAemia, CMV DNAemia requiring pre-emptive therapy and CMV-D will be treated as time-dependent co-variates.

If time-dependent covariates are to be included in the final model multivariate analyses of mortality the analysis will be performed by Cox proportional hazards regression model, with inclusion of those variables with a P value less than 0.1 in the prior univariate testing.

If either, early or late CMV DNAemia (included individually as time-dependent covariates) are found to have an impact on OS in the univariate analysis, semi-landmark plot will be constructed to illustrate visually the effect.

Statistical analysis of the clinical impact of CMV DNAemia at different periods of time before engraftment will be performed as described previously for early or late CMV DNAemia

All statistical analyses will be performed using SPSS version 20 (SPSS, Chicago, IL) and R version 2.12.2 (The CRAN project) with the packages survival v2.36-10, Design 2.3-0, prodlim v1.2.1 and cmprsk v2.2-221.