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POSTER ABSTRACTS

723.ALLOGENEIC TRANSPLANTATION: LONG-TERM FOLLOW-UP AND DISEASE RECURRENCE

Late CMV Disease after Hematopoietic Cell Transplantation: Significance of Post-Transplant Cyclophosphamide, Steroid Treatment and CMV Viral Load

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Introduction: Pre-emptive therapy (PET) and letermovir prophylaxis are effective in preventing CMV disease within the first 100 days after allogeneic hematopoietic cell transplantation (HCT), and are widely used worldwide. However, both strategies are associated with late-onset CMV disease. The goal of this study was to determine the period of risk, clinical manifestations, risk factors for initial and recurrent late CMV disease at key landmark time points, and its impact on mortality.
Patients and Methods: We retrospectively analyzed CMV seropositive allogeneic HCT recipients transplanted between 2001 and 2017 who survived more than 100 days post HCT. All patients underwent PCR monitoring and PET before day 100 and for patients deemed at high risk for late CMV complications continuation of PCR monitoring and PET was recommended. Data were collected via medical record review of CMV disease and viremia, PET, transplant variables such as lymphopenia, corticosteroid use, donor type, stem cell source, type of underlying disease, and outcomes for 2 years post-transplantation. Cumulative incidence curves and Cox proportional hazards models were used to evaluate time to event and risk factors for late CMV disease and mortality.
Results: Among 2155 day 100 survivors, 166 episodes of late CMV disease were observed in 144 (6.7%, 95% CI 5.7%-7.8%) patients. Most of the cases were diagnosed between day 100 and 1 year (126 cases), 40 episodes occurred within the second year (1.6% 95%CI 1.2%-2.3%) post HCT **(Figure 1**). CMV gastrointestinal (GI) disease (3.4%, 95% CI 2.7%-4.2%) was the most common manifestation of late CMV disease, followed by CMV pneumonia (2.9%, 95% CI 2.2%-3.7%), occurring at a median of 196 days after HCT for first GI disease episode (range 104-685) and 211 days (range 105-574) for first late pneumonia.
Twenty-nine patients (10.5%, 95% CI 7%-14.7%) developed recurrent CMV disease. Most recurrences involved the same anatomical site as the first episode with a median of 126 days (range 52-444) after the initial event. Five patients developed a third episode, with a median of 145 (range 85-350) days after their second episode.
Prolonged CMV surveillance was recommended in 1787 (83%) cases. High risk patients included: cord blood recipients , *in vivo* T-cell depletion, acute or chronic GvHD requiring steroid treatment, or those who were treated due to CMV infection before day 100. Based on day 100 risk stratification, cumulative incidence of late CMV disease occurred in 7.6% (95% CI 6.4%-8.9%) and 2.8% (95% Ci 1.4%-4.8%) in high and low risk groups, respectively. In a subgroup analysis (HCT 2001-2011), adherence to late CMV surveillance recommendations was reduced: by week 20 post-HCT, approximately 6 weeks post-discharge, only 65% of patients had CMV PCR tests performed. By 1-year post-HCT, only 40% of patients were still being tested.
In multivariable analyses, steroid treatment after day 100 at a dose of ≥1mg/kg, post-transplant cyclophosphamide, GvHD prior day 100, and CMV viremia before day 100 were associated with increased risk of late CMV disease. **(Figure 2).** The only factors contributing to recurrence of CMV disease were HLA mismatched donor status (aHR 2.92, 95% CI 1.03-8.28) and treatment with high dose steroids ≥1mg/kg after day 100 (as time dependent variable) (aHR 7.60, 95% CI 3.32-17.4). In a landmark analysis of 1-year survivors, the risk of late CMV disease was increased in chronic GvHD patients (aHR 2.11, 95% CI 0.99-4.51, p=0.054) and those with a CMV disease episode prior to 1 year (aHR 2.80, 95% CI 1.23-6.40).
Among 144 patients with late CMV disease, 32 (22%) died within 6 weeks of diagnosis of the last episode. Patients who developed late CMV pneumonia were at the highest risk of death by year 2 after HCT (aHR 4.08, 95% CI 2.62-6.35), while GI disease was associated with a somewhat lower risk (aHR 1.62, 95% CI 1.05-2.5).
Conclusion: In a large cohort for which late surveillance and PET was recommended, late CMV disease occurred frequently, and was associated with the use of high dose steroids, post-transplant cyclophosphamide, and CMV reactivation before day

100. Late CMV pneumonia and GI disease were associated with overall mortality. Improved strategies to prevent late CMV disease are needed in high-risk patients, including continued antiviral prophylaxis or surveillance strategies that are more suitable for the late setting, such as home-based CMV testing.

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Figure 1. Cumulative incidence of first late CMV disease among day 100 survivors, including organ-specific clinical manifestations.

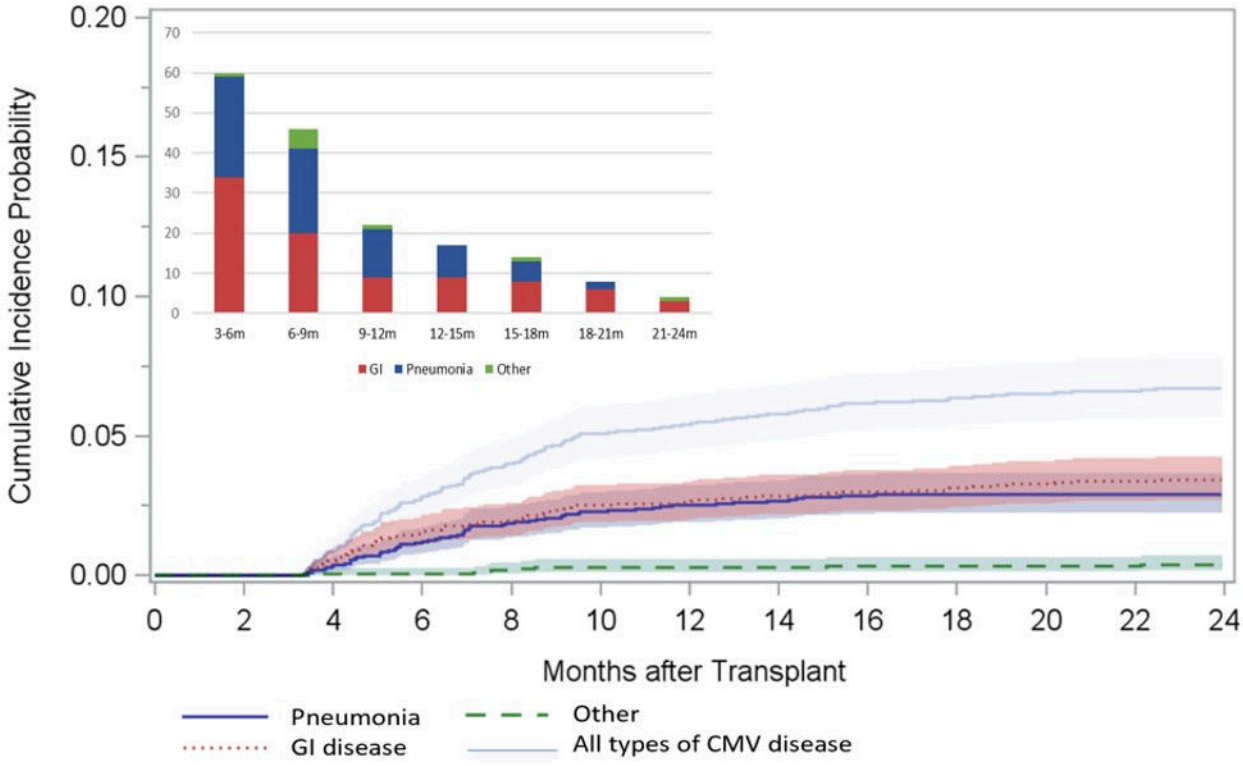

Figure 2. Multivariable Cox regression with adjusted risk factors for first late CMV disease by 2 year after transplant* **Model included age, stem cell source, conditioning regimen, CMV disease before day 100 (factors not significant with p>0.1, not shown in Figure 2) ** low risk viremia: PCR<1000 copies/ml Ag<10 positive cells, high risk viremia PCR≥1000copies/ml, Ag≥10 positive cells.*

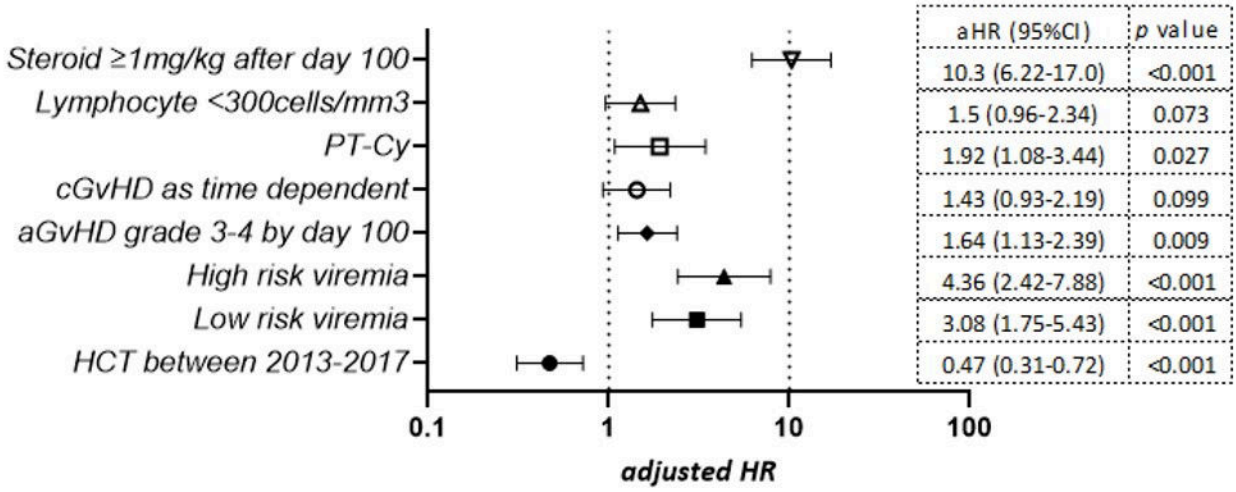

Figure 1

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