#2109

IDWeek

HHV-6 and EBV Reactivation after Allogeneic Hematopoietic Cell Transplantation in the Era of Letermovir for CMV Prophylaxis: A Retrospective Cohort Study

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Background

- The timing and risk factors for HHV-6 and CMV reactivation after allogeneic hematopoietic cell transplantation (HCT) largely overlap (**Figure 1**), and the antivirals used for CMV preemptive treatment are the first line treatments for HHV-6 encephalitis.
- An inadvertent prophylactic effect of CMV preemptive antiviral therapy on HHV-6 and EBV has been previously suggested (*Hill J.A. et al. Clin Infect Dis 2018*).
- **The advent of letermovir** for CMV prophylaxis in allogeneic HCT recipients has led to a **decreased utilization of broad-spectrum antivirals** for CMV and could result in **more frequent reactivation of herpesviruses not targeted by letermovir**.
- Moreover, recent changes in clinical practice, such as the increasing use of post-HCT cyclophosphamide for GVHD prophylaxis, have been linked to a higher incidence of non-CMV herpesvirus infections mainly driven by HHV-6.
- Letermovir was implemented at our center in October 2018.
- We **hypothesized** that the cumulative incidence of HHV-6 and EBV reactivation would increase following the introduction of LTV.
- **Objective**: To assess the cumulative incidence of HHV-6 and EBV reactivation and associated diseases within 100 days after HCT, before and after the implementation of prophylactic letermovir in our center.

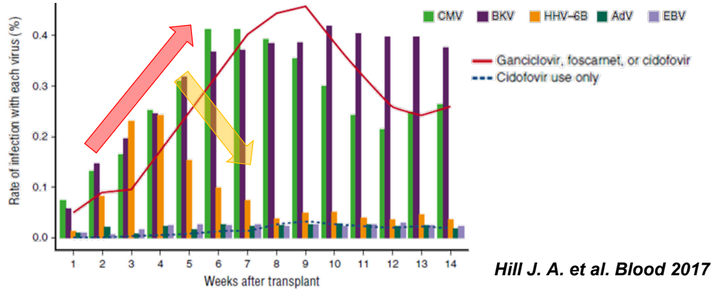


Figure 1. Double-stranded DNA viruses after allogeneic HCT in the pre-letermovir era.

Methods

- We conducted a retrospective study among CMV-seropositive adults who received a first allogeneic HCT at our center prior to and after the routine use of letermovir in 10/2018:
- **"pre-letermovir"** or **"older cohort"**: 5/2015 – 9/2018
- **"letermovir"** or **"recent cohort"**: 10/2018 – 12/2021.
- We reviewed medical records for antiviral use, viral testing, and virus-associated end-organ disease within days 0-100 after HCT.
- Testing was performed at the discretion of healthcare providers or according to treatment protocols.
- We computed cumulative incidence estimates treating death and subsequent HCT as competing risks.

Results

Table 1: Patients' characteristics

	Total n=781	Pre-letermovir cohort n=403	Letermovir cohort n=378
Days of FUP; median (range)	100 (7-100)	100 (7-100)	100 (9-100)
Demographics			
Age, years (median, IQR)	56 (42.9, 64.7)	55.7 (42.9, 64.7)	56.5 (42.9, 64.8)
Sex female	363 (46.5)	185 (45.9)	178 (47.1)
Underlying Disease			
Acute leukemia	421 (53.9)	216 (53.6)	205 (54.2)
Chronic leukemia	62 (7.9)	33 (8.2)	29 (7.7)
Myelodysplastic syndrome	197 (25.2)	94 (23.3)	103 (27.3)
Aplastic Anemia	30 (3.8)	15 (3.7)	15 (4)
Lymphoma	34 (4.4)	25 (6.2)	9 (2.4)
Plasma cell disorders	25 (3.2)	15 (3.7)	10 (2.7)
Other	12 (1.5)	5 (1.2)	7 (1.9)
CMV serostatus: D–/R+	348 (44.6)	174 (43.2)	174 (46)
HCT type			
HLA-matched related	169 (21.6)	96 (23.8)	73 (19.3)
HLA-matched unrelated	399 (51.1)	197 (48.9)	202 (53.4)
Haploidentical	60 (7.7)	27 (6.7)	33 (8.7)
HLA-mismatched unrelated	63 (8.1)	34 (8.4)	29 (7.7)
Umbilical cord blood	90 (11.5)	49 (12.2)	41 (10.9)
Myeloablative conditioning regimen	267 (34.2)	136 (33.8)	131 (34.7)
GVHD prophylaxis			
Cyclophosphamide regimen	126 (16.1)	41 (10.2)	85 (22.5)
Sirolimus containing regimen	186 (23.8)	63 (15.6)	123 (32.5)

Cumulative incidence of antiviral use by cohort

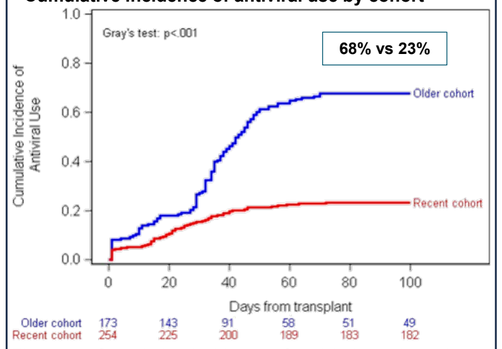


Figure 2. Cumulative incidence of antiviral use in patients with available data (older cohort: 173/403, recent cohort: 254/378).

Maximum plasma HHV-6 viral load per patient

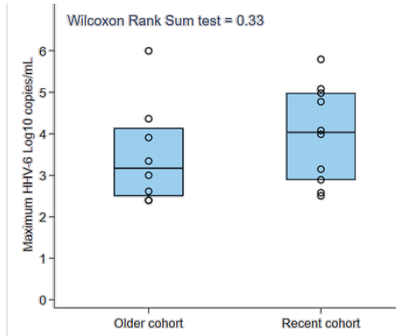
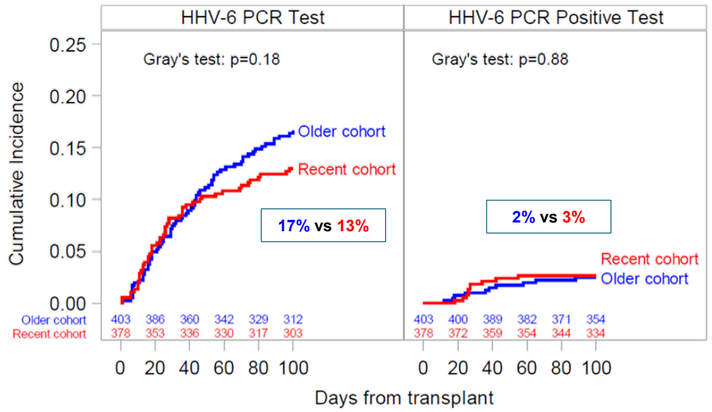


Figure 3. Maximum viral load per patient among patients with at least one positive test (n=8 in older cohort, n=10 in recent cohort).

A. Cumulative incidence of HHV-6 testing and HHV-6 reactivation



B. Cumulative incidence of EBV testing and EBV reactivation

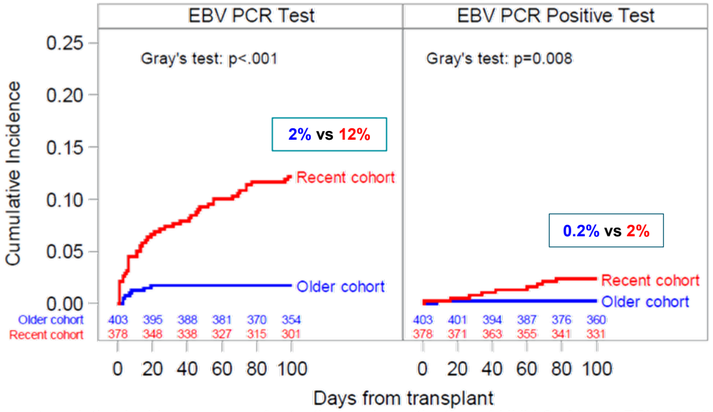


Figure 4: Cumulative incidence curves for testing and reactivation of HHV-6 (**A**) and EBV (**B**). Curves for reactivation of HHV-6 and EBV include all patients (tested and not tested). HHV-6 encephalitis developed in 2 patients in each cohort. There were no cases of PTLD by day 100 in either cohort. Gray's test was used to test for differences between curves.

Conclusions

- Despite a ~50% decrease in broad-spectrum antiviral use after the introduction of LTV prophylaxis in CMV-seropositive allogeneic HCT recipients, there was no evidence for increased HHV-6 reactivation and associated end-organ diseases.
- Whether the higher peak HHV-6 viral load in the LTV cohort has clinical implications requires further study.