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A prospective multicenter study of HHV-6B genomic DNA and gene transcription in paired bronchoalveolar lavage fluid and blood from HCT recipients

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Abstract

Background

➢ We previously demonstrated frequent detection of HHV-6B DNA in bronchoalveolar lavage fluid (BALF) and its positive association with mortality in HCT recipients from 1992-2015 with lower respiratory tract disease (LRTD).

➢ Whether these findings remain pertinent in contemporary patients, the additive value of testing for viral gene transcription, and the correlation of HHV-6 detection in blood and BALF, are unknown.

Methods

➢ We conducted a prospective study of allogeneic HCT recipients undergoing BAL for LRTD within 120 days of HCT at three cancer centers from 2015-2019.

➢We collected and tested paired blood and BALF for HHV-6B DNA by qPCR and HHV-6B mRNA (U38 and U90 gene transcripts) among DNA positive samples using RT-qPCR.

➢We described the detection of HHV-6B DNA and mRNA in blood and BALF, generated receiver operating characteristic (ROC) curves to determine the ability of BALF HHV-6B DNA detection to predict HHV-6B mRNA detection, and analyzed the association of HHV-6B DNA detection with mortality.

Results

➢ We enrolled 116 allogeneic HCT recipients who underwent 125 BALs (**Table 1**).

➢HHV-6B DNA was detected in 45 of 122 BALF (37%) compared to 19 of 124 (15%) plasma samples.

➢Among the 45 BALF samples with HHV-6B DNA detected, either HHV-6B mRNA transcript was detected in 22 (49%) (**Figure 1**).

➢BALF HHV-6B DNA ≥218 copies/ml had an area under the curve of 0.93 for predicting detection of BALF viral mRNA (**Figure 2**).

➢ In turn, patients with BALF HHV-6B DNA ≥218 copies/mL had increased risk for mortality and death due to LRTD within 60 days after the BAL (**Figure 3**).

➢This association remained after adjustment for age, oxygen use, and steroid use at the time of BAL in a multivariable Cox model (**Figure 3**).

Conclusions

➢ HHV-6B was detected more frequently in BALF than plasma, suggesting compartment-specific reactivation.

➢ BALF HHV-6B DNA ≥218 copies/mL had high sensitivity and specificity for detection of viral gene transcription in BALF and was associated with increased mortality, suggesting HHV-6B is a clinically impt. pulmonary pathogen after HCT.

Tables and Figures

Table 1. Demographic and Clinical Variables

	Negative HHV-6B DNA in BAL (N=71)	Positive HHV6-B DNA in BAL (N=42)	Total (N=113)
Age >60 years old	27 (38%)	16 (38%)	43 (38%)
Female sex	27 (38%)	22 (52%)	49 (43%)
HLA and donor			
Matched related	9 (13%)	7 (17%)	16 (14%)
Matched unrelated	26 (37%)	14 (33%)	40 (35%)
Mismatched related	11 (15%)	8 (19%)	19 (17%)
Mismatched unrelated	24 (34%)	12 (29%)	36 (32%)
Caucasian race	53 (75%)	33 (79%)	86 (76%)
Cell source			
Peripheral blood	51 (72%)	33 (79%)	84 (74%)
Bone marrow	16 (23%)	7 (17%)	23 (20%)
Umbilical cord blood	4 (6%)	2 (5%)	6 (5%)
Myeloablative conditioning	32 (45%)	14 (33%)	46 (41%)
Maximum steroid use pre-BAL			
None	39 (55%)	17 (40%)	56 (50%)
<2 mg/kg/day	27 (38%)	24 (57%)	51 (45%)
>=2 mg/kg/day	5 (7%)	1 (2%)	6 (5%)
Antiviral use pre-BAL	31 (44%)	16 (38%)	47 (42%)
Maximum oxygen use pre-BAL >2 L/minute	30 (42%)	21 (50%)	51 (45%)
LRTD cause			
Bacterial	7 (10%)	3 (7%)	10 (9%)
Viral	12 (17%)	6 (14%)	18 (16%)
Fungal	16 (23%)	10 (24%)	26 (23%)
IPS	14 (20%)	4 (10%)	18 (16%)
Other	9 (13%)	2 (5%)	11 (10%)
Multiple	13 (18%)	17 (40%)	30 (27%)

*3 patients who did not have a BAL excluded from table

Figure 2. ROC analysis of HHV-6B DNA viral load in BALF and any HHV-6B mRNA U38 or U90 gene detection

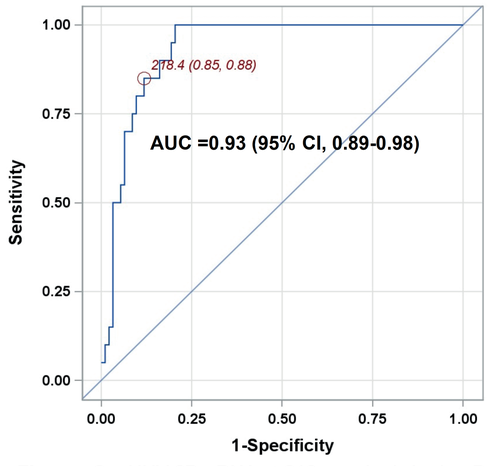


Figure 2. HHV-6B DNA ≥218 copies/mL in BALF maximizes sensitivity (85%) and specificity (88%) for the detection of HHV-6B U38 and/or U90 mRNA in BALF.

Figure 1. Distribution of HHV-6B DNA and HHV-6B mRNA detection per BAL event, stratified by categories of lower respiratory tract disease

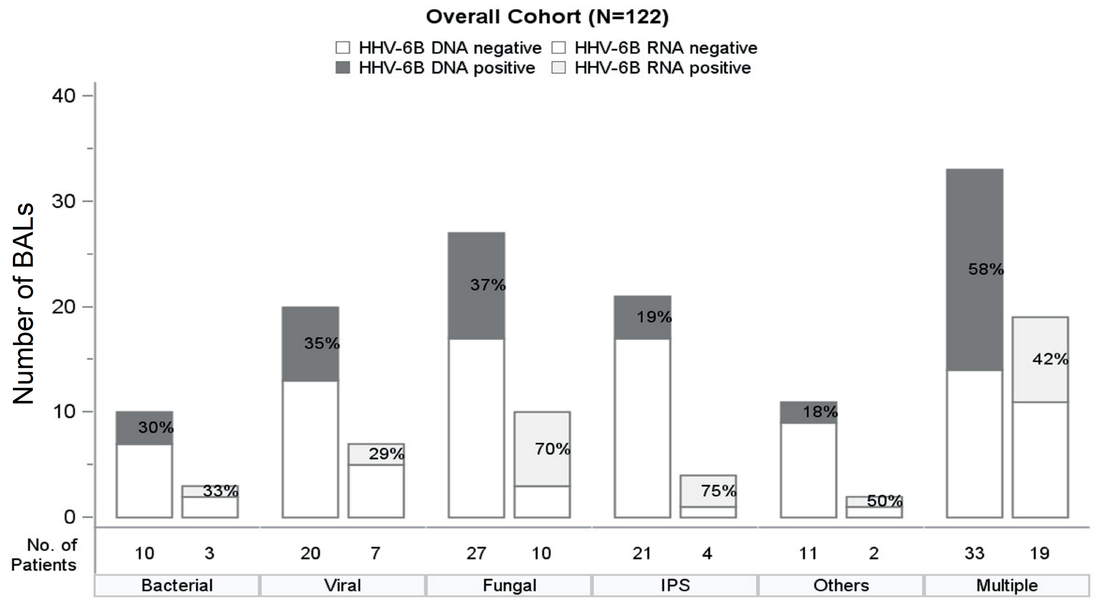
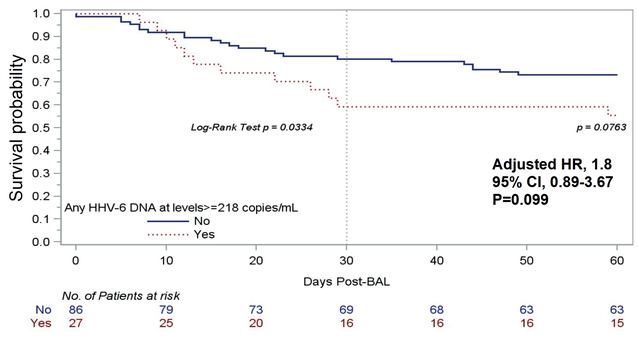


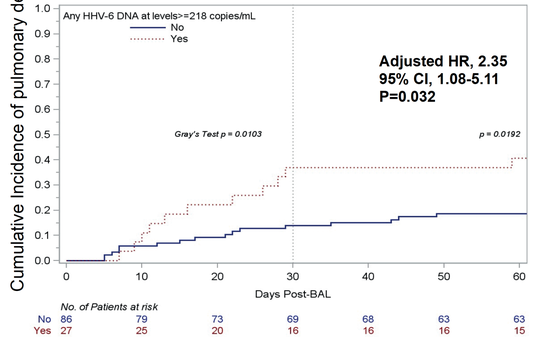
Figure 1. The X-axis indicates the clinical diagnosis category associated with each bronchoalveolar lavage (BAL) episode. The Y-axis indicates the absolute number of BALs. The first bar in each category indicates the proportion of BALs with HHV-6B DNA detection; the second bar indicates the proportion with HHV-6B mRNA detection among those with HHV-6B DNA detection.

Figure 3. Adjusted hazard ratios (HR) are from multivariable Cox models adjusted for age, oxygen use (>2 liters by nasal cannula), and steroid use at the time of the BAL.

A. Kaplan Meier plot of survival through 60 days post-BAL



B. Cumulative incidence of death from pulmonary cause through 60 days post-BAL



RELEVANT DISCLOSURES

JAH: Consulting for Allovir, Gilead, Karius, Symbio; Research support from Allovir, Gilead, Karius, Oxford Immunotec, Deverra therapeutics. **AW**: Consulting for Kyorin Pharmaceutical; Research support from Allovir, Ansun Biopharma, Pfizer, Vir/GSK. **GH:** Consulting for Generon, iTeos therapeutics, Napajen pharma, Neoleukin therapeutics; Research support from Applied molecular transport, Compass therapeutics, Heat Biologics, Laevoroc Oncology, Serplus technology, Syndax pharmaceuticals; **DMZ**: Consulting for Allovir. **MB**: Consulting for Merck. All other authors report no dislcosures.