The Journal of Infectious Diseases

LETTER TO THE EDITOR

Donor-CD4$^+$ T Cells: A Trojan Horse for Human Herpes Virus-6 After Allogeneic Hematopoietic Cell Transplantation?

To The Editor—Hanson et al [1] reported that donor-derived human herpes virus (HHV)-6B CD4$^+$ T cells are important to control HHV-6B reactivation in recipients of unmodified, matched donor, peripheral blood allografts after myeloablative conditioning. Of 33 patients studied, 10 (30%) had plasma HHV-6B detection after allogeneic hematopoietic cell transplantation (HCT) with a median peak viral load of 200 copies/mL. Patients with HHV-6 viremia ≤200 copies/mL or with no HHV-6B detection received 10-fold more donor-derived total CD4$^+$ T cells than those with peak HHV-6B detection >200 copies/mL (CD4$^+$ T cells, 1.5×10^8/kg vs 1.3×10^7/kg, respectively; $P = .047$). The role of donor-derived CD4$^+$ and, more particularly, donor-derived virus-specific CD4$^+$ in protective immunity against latent viruses after HCT is well established [2]. Recipients of cord blood allografts have rates of HHV-6 detection over 95%, plausibly due to the lack of HHV-6 specific CD4$^+$ in the cord allograft [3].

Because CD34$^+$ selected allografts contain a negligible number of donor CD4$^+$ cells, we postulated that recipients of CD34$^+$ selected allografts may have high rates of HHV-6 viremia. We examined 256 patients who received peripheral blood, CD34$^+$-selected T-cell depleted (TCD) allografts from matched donors after myeloablative conditioning at Memorial Sloan Kettering Cancer Center between 2012 and 2016. CD34$^+$ selection was performed by the CliniMACS CD34 Reagent System (Miltenyi Biotec, Gladbach, Germany), achieving a 5-log reduction of donor T cells in the allograft [4]. In our cohort, 52.3% of patients developed HHV-6 viremia post-HCT with a median maximum viral load of 1300 copies/mL (interquartile range, 484–3400) by day+100 posttransplant (Table 1). More importantly, 72 of 134 (54%) of patients with HHV-6 viremia were transient. The rate of HHV-6 viremia was higher in our cohort compared with that described by Hanson et al [1]. However, the rate of HHV-6 viremia in our cohort was comparable to the rate observed in recipients of non-TCD allografts despite the lack of donor T-cells [5–7] and lower than the rates reported in cord blood allografts [3].

Table 1. Baseline Characteristics of Patients

Characteristics	Total N = 256	HHV-6 Viremia N = 134	No HHV-6 Viremia N = 122	P Value
Age, years, median (IQR)	55.0 (44.6–63.3)	56.4 (48.4–63.6)	53.5 (42.8–63.2)	.139
Sex				.451
Female	105 (41.0%)	52 (38.8%)	53 (43.4%)	
Male	151 (59.0%)	82 (61.2%)	69 (56.6%)	
Underlying Disease				.248
Acute leukemia	128 (50.0%)	59 (44.0%)	69 (56.6%)	
Chronic leukemia/Myeloproliferative disorder	21 (8.2%)	14 (10.4%)	7 (5.7%)	
Myelodysplastic syndrome	51 (19.9%)	30 (22.4%)	21 (17.2%)	
Multiple myeloma	53 (20.7%)	30 (22.4%)	23 (18.9%)	
Nonhematologic malignancies	3 (1.2%)	1 (0.7%)	2 (1.6%)	
Donor Type				.561
Matched related donor	96 (37.5%)	48 (35.8%)	48 (39.3%)	
Matched unrelated donor	160 (62.5%)	86 (64.2%)	74 (60.7%)	
Conditioning Regimen				.077
Busulfan/Fludarabine/Melphalan	183 (71.5%)	104 (77.6%)	79 (64.8%)	
Clofarabine/Thiotepa/Melphalan	6 (2.3%)	3 (2.2%)	3 (2.5%)	
TBI/Thiotepa/Cyclophosphamide	66 (25.8%)	26 (19.4%)	40 (32.8%)	
TBI/Thiotepa/Fludarabine	1 (0.4%)	1 (0.7%)	0 (0.0%)	
Cytomegalovirus Serology				.073
Recipient negative/Donor negative	84 (32.8%)	52 (38.8%)	32 (26.2%)	
Recipient negative/Donor positive	21 (8.2%)	13 (9.7%)	8 (6.6%)	
Recipient positive/Donor negative	57 (22.3%)	28 (20.9%)	29 (23.8%)	
Recipient positive/Donor positive	94 (36.7%)	41 (30.6%)	53 (43.4%)	
HCT-CI				.045
0	54 (21.1%)	29 (21.6%)	25 (20.5%)	
1–2	88 (34.4%)	37 (27.6%)	51 (41.8%)	
3+	114 (44.5%)	29 (46.8%)	85 (43.8%)	

Abbreviations: HCT-CI, hematopoietic cell transplantation comorbidity index; HHV, human herpes virus; IQR, interquartile range; TBI, total body irradiation.

Because HHV-6 replicates predominantly in $CD4^+$, donor $CD4^+$ cells may provide a reservoir for HHV-6 replication. CD134, a member of the tumor necrosis factor superfamily, is expressed on $CD4^+$ T lymphocytes and serves as an entry receptor for HHV-6B [8]. A high CD134/CD4 ratio of HCT recipients is associated with HHV-6 reactivation after HCT [9]. Although host-derived CD4 are rare, early after myeloablative conditioning, a small number of host-derived T cells infected with HHV-6 may promote infection of donor-derived $CD4^+$ early post-HCT [9]. In contrast, the negligible number of donor-derived $CD4^+$ cells in $CD34^+$ selected TCD allografts may limit the reservoir of $CD4^+$ cells that can support HHV-6 replication and may partially explain the comparable rates of HHV-6 infection between $CD34^+$-selected TCD and unmodified allografts. Thus, although donor $CD4^+$ may act as friend and foe for HHV-6 in HCT, donor- or third party-derived HHV-6-specific T cells may be instrumental in restoring HHV-6 immunity after $CD34^+$-selected TCD HCT and warrant further study.

Notes

Financial support. This research was funded in part by National Institutes of Health (NIH) award number P01 CA23766 and NIH/National Cancer Institute Cancer Center Support Grant P30 CA008748.

Potential conflicts of interest. G. A. P. has served as an investigator for Chimerix, Astellas, Merck & Co., and Shire/Takeda and has received research grant support from Merck, Astellas, and Chimerix and consulting and other fees from Chimerix, Inc., Astellas, Merck, Cidara, Amplyx, AlloVir, Shionogi, Partners Therapeutics, ADMA Biologics, and Siemens Healthineers. She serves in a volunteer capacity as Chair of the Infectious Disease Special Interest Group of the American Society for Transplantation and Cellular Therapy (ASTCT). All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Received 22 June 2021; accepted 9 August 2021; published online August 9, 2021.

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The Journal of Infectious Diseases® 2021;XX:1–2

https://doi.org/10.1093/infdis/jiab402