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Increased Programmed Death-1 Molecule Expression in Cytomegalovirus Disease and Acute Graft-versus-Host Disease after Allogeneic Hematopoietic Cell Transplantation

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To study the role of the programmed death-1 molecule (PD-1) in cytomegalovirus (CMV) infection and disease after allogeneic hematopoietic cell transplantation (HCT), 206 subjects were followed prospectively for immune response to CMV and assigned to 3 groups based on CMV outcome. The subjects were analyzed retrospectively for PD-1 expression in cryopreserved $CD4^+$ and $CD8^+$ T cells collected at days 40, 90, 120, 150, 180, and 360 posttransplantation. HCT recipients with CMV disease (n = 14) were compared with recipients with prolonged CMV infection, but no CMV disease (median duration of infection, 3 months; n = 14) and with controls with no CMV infection who received similar transplants (n = 22). The CMV disease group had a significantly higher mean fluorescein intensity of PD-1 in $CD4^+$ ($P < .05$) and $CD8^+$ ($P < .05$) lymphocytes at all time points studied. PD-1 expression also was significantly elevated in those with severe acute graft-versus-host disease (aGVHD), including the no-viremia group. The data suggest that PD-1 is induced by aGVHD even in the absence of CMV infection. This enhanced PD-1 expression during severe aGVHD and with CMV reactivation could explain the known role of aGVHD as a risk factor for CMV disease.

Biol Blood Marrow Transplant 15: 872-880 (2009) © *2009 American Society for Blood and Marrow Transplantation*

KEY WORDS: Cytomegalovirus, PD-1, GVHD, Hematopoietic cell Transplant (HCT)

INTRODUCTION

The programmed death 1 molecule (PD-1), a member of the CD28 family, is expressed on T cells undergoing apoptosis [1]. PD-1 interacts with the ligands PD-L1 (B7-H1) and PD-L2 (B70DC), members of the B7 family, producing negative inhibitory effects on T cell function [2,3]. Multiple hematopoietic cell types, including $CD4^+$ T cells, $CD8^+$ T cells, natural killer (NK) T cells, B cells, and monocytes, express PD-1, and the physiological effects of PD-1 are only beginning to be understood. It is known that a negative immunoregulatory signal leading to loss of T cell effector function is similar to other immunoinhibitory receptors (eg, CD72, FcγRIIB, KIR), and that the cytoplasmic PD-1 domain contains similar motifs, the immunoreceptor tyrosine-based inhibitory motif and the immunoreceptor tyrosine-based switch motif [4]. On activation, PD-1 triggers a cellular cascade involving phosphatases, which counter the kinases associated with T cell receptor activation pathways, thereby decreasing T cell activation, cytokine production, and, ultimately, T cell function [1,5,6].

The role of PD-1 in graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplantation (HCT) has been studied in mouse models, which indicate that PD-1 plays a role in tissue-specific regulation of allogenic responses [7-9]. The role of PD-1–PD-L1 in T cell–mediated alloreactions appears to involve interaction with regulatory T (Treg) cells. PD-1–PD-L1 activation permits a protective effect of Tregs, which is abrogated with PD-1 blockade [10]. To date, there has been no description of PD-1 expression during GVHD in humans. Because acute and

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Financial disclosure: See Acknowledgments on page 879.

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Received December 24, 2008; accepted March 31, 2009
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1083-8791/09/157-0001$36.00/0
doi:10.1016/j.bbmt.2009.03.022

chronic GVHD (aGVHD, cGVHD) in human HCT are associated with T cell dysfunction, GVHD is considered a risk factor for viral [11,12] and fungal infections [13]. In addition, GVHD is treated with immunosuppressive agents, thus creating iatrogenic influences that undoubtedly contribute to the risk for infection. The up-regulation of PD-1 during aGVHD in HCT recipients could play a role in the pathogenesis of infection.

The concept of a loss of T cell function during persistent antigenic challenge was observed in a murine model of persistent lymphocytic choriomeningitis virus [14,15], and evaluation of this model led to an investigation of the role of PD-1 expression as a mediator of this T cell dysfunction. Reversal of T cell dysfunction in this model, using antibody to PD-L1, confirmed the role of PD-1–PD-L1 interaction in this process [16]. PD-1–associated T cell exhaustion has been implicated in human immunodeficiency virus (HIV) infection [17-23], hepatitis C virus (HCV) infection [24,25], and hepatitis B virus (HBV) infection [26]. Of note, HIV-infected subjects exhibited elevated PD-1 expression on some, but not all, HIV tetramer–specific cells and on Epstein-Barr virus (EBV)–specific but not cytomegalovirus (CMV) tetramer–specific cells [20,21], suggesting an antigen and epitope specificity to the variation in PD-1 induction. However, PD-1 expression has been shown to be increased in liver transplant recipients with CMV infection and disease [27] and in renal transplant recipients with CMV viremia [28]. The role of the PD-1 response during CMV infection in the HCT setting remains to be determined.

PATIENTS AND METHODS

Patients

A total of 206 consecutive allogeneic HCT recipients who were considered at risk for CMV infection (based on detection of CMV antibody in donor or recipient), and who underwent transplantation between 2001 and 2006, were followed prospectively for CMV infection and CMV-specific immunity in $CD4^+$ and $CD8^+$ T cells at days 40, 90, 120, 150, 180, and 360 days posttransplantation (day 0 = day of stem cell infusion). PD-1 expression was determined in cryopreserved peripheral blood mononuclear cells (PBMCs) from HCT recipients documented to have CMV disease, prolonged CMV viremia, or no CMV infection. All subjects were enrolled with the approval of the City of Hope's Institutional Review Board for prospective evaluation of CD4 and CD8 immunity and CMV infection. The Institutional Review Board also granted permission for further analysis of unused frozen specimens for PD-1 analysis.

Table 1 summarizes characteristics of the HCT recipients studied for PD-1 expression. HCT recipients were grouped as follows. The primary group, designated the CMV disease (CD) group (n = 14), comprised all subjects with documented CMV disease, as defined by Ljungman et al. [29]. In all cases, diagnosis was based on correlation of clinical events and documentation of CMV in either bronchoalveolar lavage (BAL) or tissue biopsy specimens by histology or tissue culture. The second group, the prolonged viremia (PV) group (n = 14), comprised all subjects with delayed clearance of CMV DNA in plasma as measured by polymerase chain reaction (PCR) assay after CMV infection, which required at least 8 positive assays for CMV DNA in plasma over approximately 3 months. The case control group, designated the nonviremia (NV) group (n = 22), comprised HCT recipients who underwent transplantation around the same time as those in the CD and PV groups and had no evidence of CMV reactivation after the CMV surveillance period. All other nonviremic subjects from the 2001-2006 study population (n = 30) also were analyzed for PD-1 as a control for GVHD-related factors other than CMV that might influence PD-1 expression.

Table 1. Patient Demographic for Each Group

	NV (n=22)	PV (n=14)	CD (n=14)	*P*-value
Patient age year median (range)	46 (21-59)	45 (22-62)	44 (26-64)	.97*
Donor age year median (range)	44 (20-58)	43 (27-64)	39 (19-58)	.16*
Donor status				
Sibling	16 (73%)	7 (50%)	7 (50%)	.27†
Unrelated donor	6 (27%)	7 (50%)	7 (50%)	
Hematopoietic progenitor cell source				
Bone marrow	5 (23%)	2 (14%)	0	.16†
Peripheral blood	17 (77%)	12 (86%)	14 (100%)	
Diagnosis				
Lymphoid malignancy	10 (45%)	7 (50%)	6 (43%)	.89†
Myeloid malignancy	11 (50%)	6 (43%)	6 (43%)	
Other	1 (5%)	1 (7%)	2 (14%)	
Conditioning regimen				
Myeloablative	14 (64%)	10 (71%)	8 (57%)	.73†
Nonmyeloablative	8 (36%)	4 (29%)	6 (43%)	
CMV serology				
D+/R+	15 (68%)	10 (71%)	7 (50%)	.73†
D+/R-	3 (13%)	1 (7%)	3 (21%)	
D-/R+	4 (18%)	3 (21%)	4 (29%)	

NV indicates nonviremia; PV, prolonged Viremia.
*Kruskal-Wallis test.
†Fisher's exact test or χ^2-square test.

CMV Surveillance

CMV surveillance was done twice weekly from day +21 to day +100 post-HCT, using a shell vial assay. Preemptive ganciclovir therapy was implemented based on the presence of a single CMV-positive shell vial culture [30]. CMV plasma DNA quantitative PCR (qPCR) was performed on plasma collected from the same blood specimen using the CMV gB DNA as an amplification product, as described previously [31]. Additional CMV surveillance was done beyond day +100 in "high-risk" recipients based on

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