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Clinical Research

Protective Effect of Cytomegalovirus Reactivation on Relapse after Allogeneic Hematopoietic Cell Transplantation in Acute Myeloid Leukemia Patients Is Influenced by Conditioning Regimen

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A B S T R A C T

Cytomegalovirus (CMV) reactivation after allogeneic hematopoietic cell transplant (allo-HCT) has been associated with a reduced risk of relapse in patients with acute myeloid leukemia (AML). However, the influence of the conditioning regimen on this protective effect of CMV reactivation after allo-HCT is relatively unexplored. To address this, we evaluated the risk of relapse in 264 AML patients who received T cell–replete, 6/6 HLA matched sibling or 10/10 HLA matched unrelated donor transplantation at a single institution between 2006 and 2011. Of these 264 patients, 206 received myeloablative (MA) and 58 received reduced-intensity conditioning (RIC) regimens. CMV reactivation was observed in 88 patients with MA conditioning and 37 patients with RIC. At a median follow-up of 299 days, CMV reactivation was associated with significantly lower risk of relapse in patients who received MA conditioning both in univariate ($P = .01$) and multivariate analyses (hazard ratio, .5246; $P = .006$); however, CMV reactivation did not significantly affect the risk of relapse in our RIC cohort. These results confirm the protective effect of CMV reactivation on relapse in AML patients after allo-HCT reported by previous studies but suggest this protective effect of CMV reactivation on relapse is influenced by the conditioning regimen used with the transplant.

INTRODUCTION

Cytomegalovirus (CMV) is a double-stranded DNA β herpes virus that is generally of no major clinical significance in healthy immunocompetent hosts but is responsible for significant morbidity and mortality in immunocompromised patients [1,2]. In patients with allogeneic hematopoietic cell transplant (allo-HCT), the incidence of CMV disease has been significantly reduced because of early detection of CMV reactivation and use of pre-emptive antiviral therapy. In spite of this, CMV reactivation remains a significant cause for morbidity and mortality among allo-HCT patients [3-5]. Interestingly, in a recent study by Elmaagacli et al. [6], early CMV pp65 antigenemia after allo-HCT was associated with reduced risk of relapse in acute myeloid leukemia (AML) patients. This study included a relatively homogeneous population who underwent fully matched allo-HCT with myeloablative (MA) conditioning. In a large cohort of patients, using CMV pp65 antigenemia monitoring, Green et al. [7] found a modest protection against relapse in AML patients after allo-HCT, which included both MA and reduced-intensity conditioning (RIC) patients, but the cohorts were analyzed together with no subgroup analysis. Currently, the influence of conditioning regimen on this protective effect of CMV reactivation on the risk of relapse is relatively unexplored. Quantitative CMV PCR (qPCR) is a more sensitive assay compared with pp65 antigenemia for CMV detection and has been shown to assist in early detection of CMV reactivation after allo-HCT, leading to prompt pre-emptive treatment of CMV viremia [3,8,9]. Whether implementing CMV qPCR instead of pp65 antigenemia assay alters this association of reduced relapse risk with CMV reactivation after allo-HCT in AML patients is also currently not known. To address these questions, we retrospectively analyzed 264 AML patients who received T cell–replete, 6/6 HLA matched sibling or 10/10 HLA matched unrelated donor transplantation at a single institution between 2006 and 2011.

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METHODS

Study Population

The study included a total of 382 consecutive AML patients who underwent allo-HCT at Washington University Medical Center at St. Louis between January 2006 and December 2011. This study was approved by the

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Table 1
Patient, Donor, and Transplant Characteristics

	All Patients	Patients with CMV Reactivation	Patients without CMV Reactivation	*P*
Number of patients	264	125	139	—
Median patient age, yr (range)	—	56 (23-73)	51 (17-68)	.005
Patient sex (%)				.805
Female	125 (47)	58 (46)	67 (48)	
Male	139 (53)	67 (54)	72 (52)	
Donor sex (%)				.696
Female	88 (33)	40 (32)	48 (35)	
Male	158 (67)	85 (68)	91 (65)	
Donor–patient sex				.397
Female–male	40 (15)	15 (12)	25 (18)	
Other	224 (85)	110 (88)	114 (82)	
Donor–patient CMV status (%)				<.0001
Negative–negative	94 (36)	11 (9)	83 (60)	
Negative–positive	73 (28)	59 (48)	14 (10)	
Positive–negative	25 (9)	8 (7)	17 (12)	
Positive–positive	68 (26)	44 (36)	24 (17)	
Unknown	4 (1)			
Disease etiology				.215
De novo	201 (76)	96 (77)	105 (75)	
Secondary	42 (16)	16 (13)	26 (19)	
Therapy related	21 (8)	13 (10)	8 (6)	
Transplant type (%)				.803
MRD	108 (41)	50 (40)	58 (42)	
MUD	156 (59)	75 (60)	81 (58)	
Conditioning regimen (%)				
MA	206 (78)	88 (70)	118 (85)	.005
RIC	58 (22)	37 (30)	21 (15)	
Disease classification by cytogenetics (%)				.089
Favorable	25 (9)	17 (14)	8 (8)	
Intermediate	157 (60)	70 (57)	87 (46)	
Poor	78 (30)	35 (29)	43 (44)	
Unknown	4 (1)			
Disease status at transplant (%)				.339
CR1	135 (51)	69 (55)	66 (48)	
CR2	58 (22)	29 (23)	29 (21)	
Active disease	50 (19)	29 (15)	31 (22)	
Other	21 (8)	8 (6)	13 (9)	
aGVHD (%)				.446
Grades 0-I	164 (63)	81 (65)	83 (60)	
Grades II-IV	100 (37)	44 (35)	56 (40)	
cGVHD (%)				.602
No	172 (65)	84 (68)	88 (64)	
Yes	89 (34)	40 (32)	49 (36)	
Unknown	3 (1)			
ATG regimen (%)				.009
Yes	46 (17)	30 (24)	16 (12)	
No	218 (83)	95 (76)	123 (88)	
Stem cell source				.823
Peripheral blood	240 (91)	115 (92)	125 (91)	
Bone marrow	23 (9)	10 (8)	13 (9)	
Immune prophylaxis				.023
MTX, MMF, tacrolimus	30 (11)	21 (17)	9 (6)	
MTX, tacrolimus	215 (81)	97 (78)	118 (85)	
Other*	19 (7)	7 (5)	12 (9)	

MRD indicates matched related donor; MUD, matched unrelated donor; CR, complete remission; MTX, methotrexate; MMF, mycophenolate mofetil.
* Other includes cyclosporine, MTX, sirolimus, and tacrolimus.

Table 2
Patient, Donor, and Transplant Characteristics by Intensity of Conditioning Regimen

	All Patients	MA	RIC	*P*
Number of patients	264	125	139	—
Median patient age, yr (range)	—	50 (17-68)	62 (21-73)	<.0001
Patient sex (%)				1.0
Female	125 (47)	98 (48)	27 (47)	
Male	139 (53)	108 (52)	31 (53)	
Donor sex (%)				.432
Female	88 (33)	66 (68)	22 (38)	
Male	176 (67)	140 (32)	36 (62)	
Donor–patient sex				.755
Female–male	40 (15)	29 (14)	11 (19)	
Other	224 (85)	177 (86)	47 (81)	
Donor–patient CMV status (%)				.0501
Negative–negative	94 (36)	82 (40)	12 (21)	
Negative–positive	73 (28)	54 (27)	19 (34)	
Positive–negative	25 (9)	17 (8)	8 (14)	
Positive–positive	68 (26)	51 (25)	17 (30)	
Unknown	4 (1)			
Disease etiology				.443
De novo	201 (76)	158 (77)	43 (74)	
Secondary	42 (16)	30 (14)	12 (12)	
Therapy related	21 (8)	18 (9)	3 (5)	
Transplant type (%)				.291
MRD	108 (41)	88 (43)	20 (34)	
MUD	156 (59)	118 (57)	38 (66)	
CMV reactivation				.005
Yes	206 (78)	88 (43)	37 (64)	
No	58 (22)	118 (57)	21 (36)	
Disease classification by cytogenetics (%)				.154
Favorable	25 (9)	23 (11)	2 (3)	
Intermediate	157 (60)	118 (58)	39 (67)	
Poor	78 (30)	61 (30)	17 (29)	
Unknown	4 (1)			
Disease status at transplant (%)				.012
CR1	135 (51)	100 (48)	35 (60)	
CR2	43 (22)	43 (21)	15 (26)	
Active disease	50 (19)	47 (23)	3 (5)	
Other	21 (8)	16 (8)	5 (9)	
aGVHD (%)				.015
Grades 0-I	164 (63)	120 (58)	44 (76)	
Grades II-IV	100 (37)	86 (42)	14 (24)	
cGVHD (%)				.273
No	172 (65)	130 (64)	42 (72)	
Yes	89 (89)	73 (36)	16 (28)	
Unknown	3 (1)			
ATG regimen (%)				<.0001
Yes	46 (17)	2 (1)	44 (76)	
No	218 (83)	204 (99)	14 (24)	
Stem cell source				.429
Peripheral blood	240 (91)	185 (90)	55 (95)	
Bone marrow	23 (9)	20 (10)	3 (5)	
Missing information	1			
Immune prophylaxis				<.0001
MTX, MMF, tacrolimus	30 (11)	7 (3)	23 (40)	
MTX, tacrolimus	215 (81)	181 (88)	34 (58)	
Other*	19 (7)	18 (9)	1 (2)	

MRD indicates matched related donor; MUD, matched unrelated donor; CR, complete remission; MTX, methotrexate; MMF, mycophenolate mofetil.
* Other includes cyclosporine, MTX, sirolimus, and tacrolimus.

Institutional Review Board of Washington University School of Medicine, St. Louis.

Patient demographics and transplant characteristics were prospectively entered into the Washington University School of Medicine, Blood and Marrow transplant database. Of the 382 patients, 264 were selected for the analysis based on following eligibility criteria: (1) 10/10 match at HLA loci A, B, C, DRB1, and DQB1 by high-resolution genotyping in unrelated transplantation [10] and by low resolution [11] in related donor transplantation; (2) use of unmodified donor stem cells; (3) no use of prophylactic donor lymphocyte infusion during the post-transplantation course among patients without leukemic relapse; (4) bone marrow biopsy done within 30 days before transplantation to determine the disease status at the time of transplantation; and (5) recipients of a second transplant were excluded from the study group as prior transplantation.

The type of conditioning regimen patients received was classified according to consensus definition of conditioning regimen intensity [12]. For our study, RIC and non-MA regimens were grouped together under the RIC cohort.