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Effect of Cytomegalovirus Reactivation on Relapse after Allogeneic Hematopoietic Stem Cell Transplantation in Pediatric Acute Leukemia

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A B S T R A C T

Recent studies have demonstrated the protective effect of cytomegalovirus (CMV) reactivation against relapse after allogeneic hematopoietic stem cell transplantation (HSCT) for adult myeloid malignancies. We assessed the association of CMV reactivation, defined as the development of CMV antigenemia (at least 1 pp65 antigen-positive cell per 5.0×10^4 WBCs) within 100 days after HSCT, with the risk of relapse in 143 patients with pediatric acute leukemia. The median age at HSCT was 7 years, and underlying diseases included acute lymphoblastic leukemia in 101 patients and acute myeloid leukemia in 42. The cumulative incidence of CMV reactivation at day 100 after HSCT was 45.4%. At a median follow-up of 88 months, patients with CMV reactivation had significantly lower 5-year cumulative incidence of relapse compared with patients without CMV reactivation. In a multivariate analysis, high-level CMV reactivation ($\geq$10 pp65 antigen-positive cells) was an independent factor associated with reduced relapse. However, CMV reactivation was also associated with higher nonrelapse mortality (NRM), mostly caused by opportunistic infection after grades II to IV acute graft-versus-host disease (GVHD), which resulted in decreased probability of survival. High-level CMV reactivation was a risk factor for increased NRM and worse overall survival in multivariate analysis. Although CMV reactivation may reduce the risk of relapse after HSCT for pediatric acute leukemia, effective management of severe acute GVHD and better prophylaxis and treatment of opportunistic infections are required to reduce the incidence of NRM and improve survival. Further studies on pediatric HSCT that include a larger number of patients and more homogenous patient cohorts are desirable.

INTRODUCTION

Cytomegalovirus (CMV) infection is 1 of the most important complications after allogeneic hematopoietic stem cell transplantation (HSCT). Because of the early detection of CMV reactivation together with preemptive antiviral therapy, the incidence of CMV disease after HSCT has been remarkably reduced, making it a rare cause of nonrelapse mortality (NRM) [1,2]. Nevertheless, CMV reactivation remains a significant factor associated with increased NRM after HSCT [1-4], due to indirect adverse effects including virally mediated immunosuppression, antiviral drug-induced toxicity, or increased risk of acute graft-versus-host disease (GVHD) [1,5].

The impact of pretransplantation donor and recipient CMV serostatus on HSCT outcomes remains controversial [1,6-8]. In a report on HSCT for pediatric acute leukemia and myelodysplastic syndrome, Behrendt et al. [9] showed significantly reduced risk of relapse in patients with positive donor and/or recipient CMV serostatus, which resulted in improved relapse-free survival compared with patients with negative CMV serostatus of both donor and recipient. More recently, several studies demonstrated that CMV reactivation after HSCT was associated with reduced risk of relapse, mostly in adult patients with acute myeloid leukemia (AML) [10-12] and chronic myeloid leukemia (CML) [13]. Enhanced antileukemic response by $NKG2C^+CD57^+$ natural killer cells up-regulated with CMV reactivation has been proposed as a mechanism to explain this decreased relapse after HSCT for myeloid malignancies [14]. Another possible mechanism is the cytotoxic effect of activated CMV-specific T cells after CMV reactivation, because leukemic blasts could harbor CMV and express CMV antigens [15].

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Contrary to findings in adult HSCT recipients, Jeljeli et al. [16] reported that CMV reactivation before day 120 after HSCT was associated with increased risk of relapse in children with acute leukemia. The protective effect of CMV reactivation on relapse after HSCT has not yet been confirmed in pediatric hematologic malignancies. The present study aimed to assess whether CMV reactivation after HSCT reduces the risk of relapse in children with acute leukemia. Additionally, we assessed whether the effect of CMV reactivation on relapse is altered by disease risk or the presence of severe acute GVHD.

METHODS

Patients

A total of 208 patients received allogeneic HSCT for pediatric acute leukemia in our center between 1995 and 2014. All patients or their guardians provided written informed consent to all aspects of the HSCT procedure. The present study included patients with acute lymphoblastic leukemia (ALL) and AML who received myeloablative conditioning, achieved successful engraftment, and survived without relapse more than 100 days after HSCT. Patients with secondary or therapy-related leukemia or who had undergone previous HSCT were excluded. In total, 143 patients were retrospectively analyzed. This retrospective study was approved by the institutional review board of the National Kyushu Cancer Center and was conducted in accordance with the principles of the Declaration of Helsinki.

Monitoring and Treatment of CMV Reactivation

All patients underwent weekly monitoring for CMV reactivation based on pp65 antigenemia, generally starting at the time of engraftment until discharge or death. Subsequently, outpatient monitoring was performed every 1 or 2 weeks for at least 100 days after HSCT and continued monthly until at least 1 year after HSCT. Prophylactic immunoglobulin (250 mg/kg i.v. once every 2 weeks) was administered to all inpatients. Preemptive therapy consisted of induction therapy using ganciclovir (5 mg/kg i.v. twice daily) for 2 to 3 weeks, followed by maintenance therapy with the same dose of ganciclovir once daily for 2 to 3 weeks. Patients with severe cytopenia or who were refractory to ganciclovir received foscarnet according to the treating physician's discretion.

Definitions

CMV reactivation was defined as the development of CMV antigenemia with at least 1 pp65 antigen-positive cell per 5.0×10^4 WBCs within 100 days after HSCT. High-level CMV reactivation was defined as CMV pp65 antigenemia with 10 or more pp65 antigen-positive cells per 5.0×10^4 WBCs.

Standard-risk disease was defined as the first or second complete remission (CR) at the time of HSCT. High-risk disease included third or higher CR at HSCT and non-CR at HSCT. Primary induction failure and postrelapse reinduction failure were also assigned to the high-risk disease group regardless of the status at HSCT. Relapse was defined as any evidence of leukemia irrespective of morphologic, cytogenetic, or molecular relapse after achieving CR after HSCT. NRM was defined as death due to any cause without evidence of relapse. The grades of acute and chronic GVHD were determined based on consensus criteria [17,18].

Statistical Analysis

Differences in the proportions of clinical characteristics between the 2 study groups were compared using chi-square and Fisher exact tests as appropriate. Overall survival (OS) was defined as the time from the day of HSCT to the day of last follow-up, and disease-free survival (DFS) was measured from HSCT to last follow-up or first event including relapse and NRM. To exclude bias due to including patients who died or relapsed too early to develop reactivation into the group without CMV reactivation, a 100-day landmark analysis was performed. The probabilities of OS and DFS were estimated using the Kaplan-Meier method. Univariate analysis of OS and DFS were performed using log-rank tests. Cumulative incidence of relapse and NRM were estimated on the basis of a cumulative incidence method that treated each relapse and NRM as a competing risk for the other. Groups were compared using Gray's test. Multivariate analysis was performed using the Cox proportional hazard regression model for OS and DFS and the Fine and Gray method for relapse and NRM. All statistical analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and $P < .05$ were considered statistically significant.

RESULTS

Patients and Transplantation Characteristics and CMV Reactivation

Patients and transplantation characteristics are summarized in Table 1. Patients consisted of 79 boys and 64 girls with a median age of 7 years (range, 0 to 24) at the time of HSCT. The underlying disease was ALL in 101 patients (71%) and AML in 42 (29%). Ninety-three patients (65%) were assigned to the standard-risk group and 50 (35%) were assigned to the high-risk group. Bone marrow was the most common stem cell source (n = 112, 78%) followed by cord blood (18%) and peripheral blood stem cells (3%). No patient received antithymocyte globulin as a part of the conditioning regimens.

Table 1
Patient Characteristics

	All Patients (N = 143)	Patients with CMV Reactivation (n = 65)	Patients without CMV Reactivation (n = 78)	*P*
Median age, yr (range)	7 (0-24)	9 (0-18)	7 (0-24)	
Age				.181
≤7 yr	73	29	44	
>7 yr	70	36	34	
Sex				1
Male	79	36	43	
Female	64	29	35	
Diagnosis				.144
ALL	101	50	51	
AML	42	15	27	
Disease risk				.726
Standard	93	41	52	
High	50	24	26	
Year of HSCT				.737
1995-2004	69	30	39	
2005-2014	74	35	39	
Donor				.094
Related	64	24	40	
Unrelated	79	41	38	
HLA disparity				.458
Matched	102	44	58	
Mismatched	41	21	20	
Stem cell source				.171
BM	112	52	60	
PB	5	4	1	
CB	26	9	17	
Conditioning regimen				.0223
TBI	93	50	43	
BU	32	9	23	
TBI/BU	18	6	12	
GVHD prophylaxis				.0178
Weekly MTX	15	2	13	
CsA base	50	22	28	
Tac base	78	41	37	
Donor/recipient CMV serostatus				<.01
D−/R−	18	2	16	
D+/R−	15	3	12	
D−/R+	49	27	22	
D+/R+	61	33	28	
CMV pp65 antigenemia				
<10 positive cells	—	30	—	—
≥10 positive cells	—	35	—	
Acute GVHD (≤day 100)				<.01
0-I	66	21	45	
II-IV	77	44	33	
Chronic GVHD				.0346
None or mild	103	40	63	
Moderate or severe	40	25	15	

BM indicates bone marrow; PB, peripheral blood; CB, cord blood; TBI, total body irradiation; BU, busulfan; MTX, methotrexate; CsA, cyclosporine A; Tac, tacrolimus.