Impact of Cytomegalovirus Replication and Cytomegalovirus Serostatus on the Outcome of Patients with B Cell Lymphoma after Allogeneic Stem Cell Transplantation

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A B S T R A C T

Cytomegalovirus (CMV) replication after allogeneic hematopoietic stem cell transplantation (HSCT) was historically associated with increased nonrelapse mortality (NRM). More recently, different groups have reported an association between CMV replication and reduced risk of acute myeloid leukemia (AML) relapse. Given the conflicting results, we evaluated the impact of CMV replication and other covariates on the outcome of a retrospective cohort of 265 adults with B cell lymphoma receiving allogeneic HSCT from HLA-identical siblings or alternative donors. In time-dependent multivariate analysis, CMV replication, evaluated by pp65 antigenemia, had no independent effect on the risk of relapse (hazard ratio [HR], 1.0; 95% confidence interval [CI], .6 to 1.6; $P = .9$), although it was associated with a reduced overall survival (HR, 2.0; 95% CI, 1.3 to 3.2; $P = .001$) and an increased NRM (HR, 2.5; 95% CI, 1.1 to 5.3; $P = .01$). Consistently, donor and/or recipient CMV seropositivity were not associated with a different outcome relative to CMV double-negative serostatus. In multivariate models, a diagnosis of follicular lymphoma ($P < .0001$) and pretransplantation complete remission status ($P < .0001$) were the main independent predictors for improved relapse-free survival. In summary, contrary to what is observed in patients with AML, this report identifies no independent role for CMV replication or serostatus on the relapse of patients with B cell lymphomas undergoing allogeneic HSCT.

INTRODUCTION

Patients with lymphoid malignancies who relapse after second-line chemotherapy or autologous transplantation have a dismal prognosis and very few effective options for salvage treatment. Allogeneic hematopoietic stem cell transplantation (HSCT) after myeloablative (MAC) or reduced-intensity conditionings (RIC) is the only potential curative strategy for patients with recurrent indolent or aggressive non-Hodgkin's (NHL) and Hodgkin's lymphomas (HL) [1,2].

In a prospective trial for lymphoma patients [3], we have previously identified lymphoma histotype and pre-transplantation disease status as the main independent variables affecting the risk of disease relapse and post-transplantation outcome. More recently, human cytomegalovirus (CMV) replication was found to be associated not only with higher post-HSCT nonrelapse mortality (NRM) [4], but also with a reduced risk of relapse for patients with acute myeloid leukemia (AML) [5]. This observation, in line with previous reports on the effect of CMV replication and serostatus on the outcome of patients with AML [6-8], was not confirmed in a recent retrospective analysis of subjects with other myeloid and lymphoid malignancies who underwent transplantation [9].

Given the conflicting results, we analyzed a retrospective cohort of 265 B cell lymphoma patients receiving allogeneic HSCT from HLA-identical siblings or alternative donors to investigate the potential role of post-HSCT CMV replication and pre-HSCT CMV serostatus on transplantation outcome.

PATIENTS AND METHODS

Study Design

This is a retrospective study including 265 consecutive adult B cell lymphoma patients who underwent transplantation in any 1 of 7 Italian institutions between April 1998 and November 2012. The institutional

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Table 1
Patients Characteristics According to Post-transplantation pp65 Antigenemia

Characteristics	All Patients	Patients with pp65-Antigenemia	Patients without pp65-Antigenemia	*P* Value
Patients, n	265	133 (50%)	132 (50%)	
Histologic Subtype				
Follicular non-Hodgkin lymphoma	63 (20%)	37 (57%)	27 (43%)	
Aggressive non-Hodgkin lymphoma	94 (31%)	46 (49%)	48 (51%)	.3
Chronic lymphocytic leukemia	22 (7%)	13 (59%)	9 (41%)	
Hodgkin lymphoma	84 (27%)	37 (44%)	47 (56%)	
Patient age, median (range), yr	45 (18-68)			.2
<40	101 (38%)	46 (45%)	55 (55%)	
≥40	164 (62%)	88 (53%)	76 (47%)	
Donor type				**.003**
Sibling	139 (52%)	58 (42%)	81 (58%)	
Alternative	126 (48%)	76 (60%)	50 (40%)	
Immunosuppression				.03
CSA/MTX	141 (55%)	62 (43%)	79 (57%)	
ATG or alemtuzumab	124 (45%)	71 (57%)	53 (43%)	
Donor/patient CMV serostatus				**<.0001**
Negative/Negative	28 (12%)	1 (3%)	27 (97%)	
Others	237 (88%)	132 (55%)	105 (45%)	
Disease status at HSCT				.2
CR	108 (41%)	61 (56%)	47 (44%)	
PR	92 (36%)	43 (47%)	49 (53%)	
Refractory (SD/PD)	65 (23%)	30 (46%)	35 (54%)	
Number of lines of CT				1
≤2	68 (26%)	34 (50%)	34 (50%)	
>2	197 (74%)	99 (50%)	98 (50%)	
Preparative regimen				.1
MAC	75 (26%)	43 (57%)	32 (43%)	
RIC	189 (74%)	90 (47%)	99 (53%)	
Graft source				.6
PBSC	239 (92%)	122 (51%)	117 (49%)	
BM	26 (18%)	12 (46%)	14 (54%)	
aGVHD				
No	134 (51%)	64 (48%)	68 (52%)	.5
Yes	131 (49%)	69 (52%)	62 (48%)	
Grade I-II	104	51 (49%)	53 (51%)	.6
Grade III-IV	27	15 (55%)	12 (45%)	
cGVHD				1
No	169 (65%)	66 (51%)	64 (49%)	
Yes	96 (35%)	48 (50%)	48 (50%)	
Mild	36	17 (47%)	19 (53%)	.5
Moderate	32	15 (47%)	17 (53%)	
Severe	27	16 (59%)	11 (41%)	

CR indicates complete remission; PR, partial remission; SD/PD, stable disease/progressive disease; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; CT, chemotherapy; CMV, cytomegalovirus; CSA, cyclosporine; MTX, methotrexate; ATG, antithymocyte globulin.
P value with Fisher's test.
Bold indicates significant *P* values.

review boards of the 7 hospitals approved the study. The patient population encompasses all subjects with lymphoma who received allogeneic HSCT at the fore-mentioned institutions fulfilling the following criteria: (1) graft source represented by an HLA-identical sibling or an alternative (matched unrelated donor or unmatched sibling, excluding haploidentical relatives) donor; (2) availability of complete information about HLA matching between donor and recipient at the HLA loci A, B, C, DRB1, and DQB1, through high-resolution genotyping (previously described [10]); (3) availability of pretransplantation–CMV antibody serological status of both donor and recipient; (4) availability of CMV-seronegative donors of blood product substitutions for patients and donors pairs with pretransplantation-negative CMV status; (5) regularly monitored, once or twice weekly, CMV replication by pp65-antigenemia until at least week 16 after transplantation; (6) no use of prophylactic donor lymphocyte infusion; and (7) confirmed histologic diagnosis of B cell NHL or HL. Patients with T cell lymphomas were not included, given their different outcome.

Transplantation Characteristics

The pretransplantation conditioning regimen consisted of the combination of thiotepa, either at 15 mg/kg (myeloablative) or 10 mg/kg (reduced intensity) and cyclophosphamide 60 mg/kg plus fludarabine 60 mg/m^2 in most patients (n = 159), as previously described [11]; thiotepa-cyclophosphamide plus melphalan 70 mg/m^2 in 11 subjects; and thiotepa-cyclophosphamide in 30 patients [12]. Other conditioning regimens were melphalan 140 mg/m^2 plus fludarabine 60 mg/m^2 in 13 subjects and the combination of low-dose total body irradiation with chemotherapy in the remaining 51 subjects [13]. Pharmacological prophylaxis of acute graft-versus-host disease (GVHD) consisted of oral cyclosporine and short-course methotrexate for the 139 patients who underwent transplantation from an identical sibling. One-hundred twenty-six patients received a graft from an alternative donor (8 from a mismatched sibling, 50 from an HLA-matched unrelated donor (MUD), and 68 from a mismatched MUD): these patients received further immunosuppression, either with antithymocyte globulin (ATG, Thymoglobulin, Genzyme, Europe BV, Naarden, The Netherlands) 7 mg/kg total dose on days -4 and -3 before transplantation (92 subjects) or with alemtuzumab 15 to 30 mg/m^2 (30 subjects), as previously published [13-15]. Mismatched donors comprised both antigen- or allele-mismatched transplantations at loci HLA-A, -B, -C, -DR, or -DP.

Pretransplantation disease status and response were evaluated by computed tomography or positron emission tomography and assessed according to criteria established by Cheson et al. [16]. Acute and late acute GVHD [17] and chronic or early chronic GVHD were diagnosed as previously described [18].

CMV Antigenemia and Pre-Emptive Therapy

CMV replication was detected by pp65-antigenemia positivity. Monitoring started when a white blood cell count of 500 per microliter was reached after HSCT and continued until week 16 [19]. CMV replication was