Varicella-Zoster Reactivation after Allogeneic Stem Cell Transplantation without Routine Prophylaxis—The Incidence Remains High

Ola Blennow [1,2,*], Gustav Fjaertoft [2], Jacek Winiarski [3], Per Ljungman [4], Jonas Mattsson [2], Mats Remberger [2]

[1] Division of Infectious Diseases, Department of Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
[2] Centre for Allogeneic Stem Cell Transplantation, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
[3] Department of Pediatrics, Clintec, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
[4] Division of Hematology, Department of Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

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A B S T R A C T

One-year prophylaxis with acyclovir has been shown to effectively prevent varicella-zoster virus (VZV) reactivation after allogeneic hematopoietic stem cell transplantation (HSCT) in a cohort that underwent transplantation in the beginning of the 2000s. Transplantation procedures have since changed considerably and reduced-intensity conditioning (RIC) is nowadays common. We investigated VZV reactivation without routine prophylaxis in a cohort of HSCT patients, 50% of whom had received RIC. The cumulative 2-year incidence of VZV reactivation was 20.7%. Risk factors in a multivariate analysis were treatment with mesenchymal stromal cells (relative hazard [RH], 1.65; confidence interval [CI], 1.07 to 2.54; $P = .02$), total body irradiation ≥6 Gy (RH, 1.55; CI, 1.14 to 2.13; $P = .006$), engraftment later than day 16 (RH, 1.46; CI, 1.07 to 2.00; $P = .02$), and age 0 to 19 years (RH, 1.68; CI, 1.21 to 2.35; $P = .002$). There was no difference in VZV reactivation between patients receiving myeloablative conditioning or RIC. VZV-related complications occurred in 29% of the patients with reactivation; most common were disseminated disease and postherpetic neuralgia. No single low-risk group for VZV reactivation could be identified. We conclude that VZV reactivation remains common after HSCT and carries a high complication rate, warranting prophylaxis.

INTRODUCTION

The cumulative incidence of varicella-zoster virus (VZV) reactivation (herpes zoster) after allogeneic hematopoietic stem cell transplantation (HSCT) was reported to be around 50% during the 1990s, declining to a little over 20% in the beginning of the 2000s [1-4]. Complications are common, including postherpetic neuralgia, disseminated infection, and occasional deaths [3,5-7]. One-year prophylaxis with acyclovir or valacyclovir has been shown in a large cohort study by Erard et al. to effectively prevent VZV reactivation without evidence of rebound after discontinuation [1]. However, it is important to recognize that the control cohort not given prophylaxis in the Erard study underwent transplantation more than 10 years ago, between 1998 and 2002, with only .6% of the patients receiving reduced-intensity conditioning (RIC). The 1-year cumulative incidence of VZV after RIC HSCT was reported to be lower than after myeloablative HSCT, but it has varied considerably in different studies, ranging from 10% to 27% [1,5,8]. The aim of this study was to investigate the incidence of VZV reactivation in a center performing 50% RIC HSCT and not using long-term routine VZV prophylaxis, except for patients with graft-versus-host disease (GVHD).

MATERIALS AND METHODS

Patient Population

All VZV-seropositive patients undergoing allogeneic HSCT at the Karolinska University Hospital, Huddinge, between January 2000 and August 2012, were included. Patient characteristics are presented in Table 1. The study was approved by the Research Ethics Committee of Karolinska Institutet.

Conditioning

RIC was given to 414 patients and consisted of fludarabine 30 mg/m^2/day for 3 to 6 days in combination with any of the following modalities: (1) cyclophosphamide (Cy) 60 mg/kg/day for 2 days (n = 83), (2) 2 × 3 Gy total body irradiation (TBI) and Cy 60 mg/kg/day for 2 days (n = 70), (3) 2 Gy TBI (n = 42), (4) treosulphan 14 g/m^2 for 3 days (n = 55), or (5) 4 mg/kg/day busulfan orally for 2 days (n = 164) [9-11]. Myeloablative conditioning consisted of Cy 60 mg/kg/d for 2 days in combination with either (1) 10 Gy single-fraction TBI (n = 2), (2) 4 × 3 Gy fractionated TBI (+VP16 or melphalan in 22) (n = 143), or (3) 4 mg/kg/day busulfan for 4 days (n = 230) (+VP16 or melphalan in 19) [12]. Thirteen patients with severe aplastic anemia and a sibling donor received Cy 50 mg/kg/day for 4 days. Antithymocyte globulin was given to 541 patients and alemtuzumab to 36 patients as part of the conditioning, with the last dose on the day before transplantation [13].

Prophylaxis

Acyclovir prophylaxis, 400 mg 2 times daily, was only used in patients who had an IgG antibody titer to herpes simplex virus of ≥10,000, and it was administered until the absolute neutrophil count was ≥.5 × 10^9/L [14]. Monitoring for cytomegalovirus infection was performed by PCR for cytomegalovirus DNA. The PCR methods varied during the study period [8]. Viral loads at the predetermined cut-off levels were treated preemptively using intravenous ganciclovir or oral valganciclovir [8,15]. Treatment duration in most cases was until the PCR result became negative. If this therapy failed, either because of lack of efficacy or toxicity, the patients were switched to

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* Correspondence and reprint requests: Ola Blennow, MD, Division of Infectious Diseases, I 73, Karolinska University Hospital, Huddinge, SE-141 86, Stockholm, Sweden.
E-mail address: ola.blennow@karolinska.se (O. Blennow).

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Table 1
Patient Characteristics and Risk Factor Analyses

	No VZV Infection n = 630	VZV Infection n = 172	Univariate (*P* Value)	Multivariate (HR, 95% CI, *P* Value)
Age	44 (<1-71)	34 (<1-67)	.004	1.68, 1.21-2.35, *P* = .002
Sex (M/F)	368/262	112/60	.13	
Malignancy	563 (89%)	148 (86%)	.28	
ALL or lymphoma	132 (21%)	48 (28%)	.07	
Nonmalignant disorder	67 (11%)	24 (14%)	.28	
Disease stage (early/late)*	291/287 (46/46%)	91/74 (53/45%)	.32	
Donor age	35 (0-72)	34 (0-70)	.35	
Donor				
HLA-identical related	236 (37%)	58 (34%)	.42	
MUD	324 (51%)	88 (51%)		
Mismatched (related/URD)	70 (11%) (9/61)	26 (15%) (0/26)		
Conditioning				
MAC/RIC	295/335 (47/53%)	93/79 (54/46%)	.11	
TBI-based (>6 Gy)	152 (24%)	62 (36%)	.003	1.55, 1.14-2.13 *P* = .006
Chemo-based	477 (76%)	110 (64%)		
ATG	421 (67%)	120 (69%)	.52	
Alemtuzumab	24 (3.8%)	12 (7%)	.12	
NC dose, $\times 10^8$/kg	9.6 (.2-81)	8.3 (.2-42)	.31	
CD34 dose, $\times 10^6$/kg	7.1 (.01-68)	6.7 (.03-43)	.47	
Stem cell source (BM/PBSC/CB)	145/451/34 (23/72/5%)	58/106/8 (34/62/5%)	.02	
G-CSF	155 (25%)	40 (23%)	.78	
aGVHD				
0	258 (41%)	71 (41%)	.81	
I	136 (22%)	36 (21%)	.75	
II	171 (27%)	55 (32%)	.73	
III-IV	65 (10%)	10 (6%)		
cGVHD (yes/no)†	160/402 (25%)	31/134 (18%)	.02	
CMV ser MM	234 (37%)	57 (33%)	.40	
EBV ser MM	102 (16%)	29 (17%)	.94	
MSC	53 (8%)	24 (14%)	<.05	1.65, 1.07-2.54, *P* = .02
Days to ANC > .5 (mean)	17.0	18.3	<.01	1.46, 1.07-2.00, *P* = .02

HR indicates hazard ratio; M, male; F, female; ALL, acute lymphoblastic leukemia; MUD, HLA-A, -B, and -DR matched unrelated donor; mismatch, HLA-A, -B, or -DR allele or antigen mismatch; URD, unrelated donor; MAC, myeloablative conditioning; RIC, reduced conditioning; TBI, total body irradiation; ATG, antithymocyte globulin; NC, nucleated cell; BM, bone marrow; PBSC, peripheral blood stem cell; CB, cord blood; G-CSF, granulocyte colony–stimulating factor; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; ser MM, serological mismatch; EBV, Epstein-Barr virus; ANC, absolute neutrophil count.
Absolute numbers or median and range are presented if not stated otherwise.
* Early includes first complete remission/first chronic phase and nonmalignancies; late includes beyond first complete remission/first chronic phase (patients with solid tumor not included).
† Chronic GVHD occurring before VZV.

treatment with foscarnet [16]. Acyclovir prophylaxis to prevent VZV reactivation, 400 mg 2 times daily, was recommended in patients with acute GVHD grade II or higher and/or chronic GVHD treated with immunosuppression.

Reactivation of VZV

Reactivation of VZV was based on clinical findings, in most cases confirmed by detection of VZV DNA in material from the vesicular lesions. *Dissemination* was defined as involvement of more than 1 dermatome, if not adjacent; otherwise, it was defined as involvement of more than 2 dermatomes. *Postherpetic neuralgia* was defined as pain persisting in the affected dermatome for more than 30 days after onset of reactivation.

Statistical Analysis

The incidence of VZV infection was calculated using an estimator of cumulative incidence curves. Patients were censored at the time of death or last follow-up. Predictive analyses were based on the proportional hazard model for subdistribution of competing risk. Univariate and multivariate analyses were then performed using Gray's test and the proportional subdistribution hazard regression model of Fine and Gray [17]. A stepwise backward procedure was used to construct a set of independent predictors. All predictors with a *P* value below .10 were considered and sequentially removed if the *P* value in the multiple models was above .05. All tests were 2-sided. The type I error rate was fixed at .05 for factors potentially associated with time-to-event outcomes. Categorical parameters were compared using chi-square test and continuous variables were compared using the Mann-Whitney test. Analyses were performed using the cmprsk package (developed by Gray, June 2001), Splus 6.2 software (Insightful, Seattle, WA), and Statistica software (StatSoft, Tulsa, OK).

RESULTS

Cumulative Incidence of Reactivation of VZV

The median follow-up time was 2.4 years (range, 8 to 4664 days), and 59 patients were lost to follow-up during the first year after HSCT (7.4% of all HSCTs). In all, 172 patients (21.4%) reactivated VZV at a median of 175 days after HSCT (range, 1 to 2198), resulting in a total cumulative incidence of 22.6% (Figure 1A). Most reactivations occurred during the first year, and the vast majority occurred within 2 years after HSCT (20.7%) (Figure 1A). No breakthrough infection during acyclovir prophylaxis could be identified. There was no significant difference in VZV reactivation rate per year during the study period (Figure 1B). Patients with VZV reactivation had the same overall mortality as patients with no reactivation (data not shown).

Risk Factors for VZV Reactivation

Risk factors for VZV reactivation in a multivariate regression analysis were receiving mesenchymal stromal cells (MSCs) (relative hazard [RH], 1.65; 95% confidence interval [CI], 1.07 to 2.54; $P = .02$), TBI $\geq$ 6 Gy as a part of conditioning (RH, 1.55; 95% CI, 1.14 to 2.13; $P = .006$), engraftment later than day 16 (RH, 1.46; 95% CI, 1.07 to 2.00; $P = .02$), and age 0 to 19 years (RH, 1.68; 95% CI, 1.21 to 2.35; $P = .002$). The incidence in 10-year age intervals was 24% in