Transplant Immunology 38 (2016) 60–66

Contents lists available at ScienceDirect

Transplant Immunology

journal homepage: www.elsevier.com/locate/trim

Toll-like receptor 1 variation increases the risk of transplant-related mortality in hematologic malignancies

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ARTICLE INFO

Article history:
Received 21 May 2016
Received in revised form 31 May 2016
Accepted 24 June 2016
Available online 28 June 2016

Keywords:
*TLR*1
Unrelated donor
Bone marrow transplantation
Single nucleotide variation

ABSTRACT

Toll-like receptor 1 (*TLR*1) genetic variant (rs5743551, −7202A > G) has been reported to be associated with susceptibility to various infectious diseases. We retrospectively examined the impact of *TLR*1 variation on transplant outcomes in a cohort of 320 patients who underwent unrelated HLA-matched bone marrow transplantation (BMT) for hematologic malignancies. A multivariate analysis showed that the G/G genotype in the recipients and the donors was associated with a significantly lower 3-year transplant-related mortality (TRM). The recipient G/G genotype also resulted in a better 3-year progression-free survival. This study suggests that the recipient and donor *TLR*1 G/G genotypes are comparably associated with a reduced risk of death that was not related to relapse. Thus, *TLR*1 genotyping may be useful for selecting the donor, managing patients in a risk-adapted manner, and creating therapeutic strategies to prevent complications after hematopoietic stem cell transplantation.
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1. Introduction

Toll-like receptor 1 (TLR1), which is the most ubiquitously and highly expressed member of the TLR family of pattern recognition receptors in the innate immune system, plays important roles in immune recognition of invading microbes [1,2]. A single nucleotide variation in the *TLR*1 promoter gene, rs5743551 (−7202A > G), has been shown to be capable of affecting the production of cytokines, *NF-κB* activation, and the cell surface expression of TLR1 [3]. This variation has also been associated with susceptibility to various infectious diseases caused by bacteria, fungi, human immunodeficiency virus, leprosy, tuberculosis, and malaria [3–10]. In the view of the crucial roles of TLRs in transplant-related complications, such as infections and organ damage after allogeneic hematopoietic stem cell transplantation (SCT) [11,12], we retrospectively investigated the association between *TLR*1 variation and transplant outcomes in a cohort of patients who underwent unrelated HLA-matched bone marrow transplantation (BMT) for hematologic malignancies through the Japan Marrow Donor Program (JMDP). Our data shows an

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http://dx.doi.org/10.1016/j.trim.2016.06.002
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association between the donor and recipient *TLR*1 G/G genotypes and a lower transplant-related mortality (TRM) after unrelated BMT.

2. Patients and methods

2.1. Patients

A total of 320 patients with hematologic malignancies and their unrelated donors were included in the study. The patients underwent BMT through the JMDP with T cell-replete marrow from HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 allele-matched donors between May 2006 and April 2009. No patient had a history of previous transplantation. The final clinical data analyses of these patients were completed by September 27, 2011. Diagnoses included acute myeloid leukemia (AML) (n = 146; 46%), acute lymphoblastic leukemia (ALL) (n = 76; 24%), myelodysplastic syndrome (MDS) (n = 51; 16%), malignant lymphoma (ML) (n = 32; 10%), chronic myeloid leukemia (CML) (n = 12; 4%), and myeloproliferative neoplasm (MPN) (n = 3; 1%) (Table 1). Relapse or secondary cases were defined as high-risk diseases. Myeloid malignancies included AML, MDS, CML, and MPN. Lymphoid malignancies included ALL and ML. The conditioning regimen varied according to the underlying disease and the condition of the patient. The combination of cyclophosphamide (CY) and total body irradiation (TBI), which was fractioned in all cases, was mainly used for the myeloablative conditioning (MAC) regimen, whereas the combination of fludarabine and melphalan was mainly used for the reduced-intensity conditioning (RIC) regimen [13]. Cyclosporine- or tacrolimus-based therapy was used for graft-*versus*-host disease (GVHD) prophylaxis [14,15], except one case that received only methotrexate. Patients administered *anti*-T cell therapy, such as antithymocyte globulin or *ex vivo* T cell depletion, were excluded from this study. All patients and donors provided their informed consent at the time of transplantation to participate in molecular studies of this nature according to the Declaration of Helsinki. This project was approved by the Institutional Review Board of Aichi Medical University School of Medicine and the JMDP.

Table 1
Recipient and donor characteristics
Abbreviations: TNC, total number of nucleated cells harvested.

Variable	Value
Number of cases	320
Patient age, years, median (range)	47 (1–67)
Donor age, years, median (range)	34 (20–66)
Year of HSCT, median (range)	2008 (2006–2009)
Patient *TLR*1 genotype, n (%)	
A/A	31 (10)
A/G	128 (40)
G/G	161 (50)
Donor *TLR*1 genotype, n (%)	
A/A	34 (11)
A/G	119 (37)
G/G	167 (52)
Patient sex, n (%)	
Male	187 (58)
Female	133 (42)
Donor sex, n (%)	
Male	218 (68)
Female	102 (32)
Patient/Donor sex match, n (%)	
Sex-matched	179 (56)
Female/Male	86 (27)
Male/Female	55 (17)
Disease, n (%)	
AML	146 (46)
ALL	76 (24)
MDS	51 (16)
ML	32 (10)
CML	12 (4)
MPN	3 (1)
Myeloid Malignancies	212 (68)
Lymphoid Malignancies	108 (34)
Disease stage, n (%)	
High risk	140 (44)
Standard risk	180 (56)
ABO matching, n (%)	
ABO-matched	198 (62)
Major mismatch	55 (17)
Minor mismatch	52 (16)
Bidirectional	15 (5)
Conditioning regimen, n (%)	
Myeloablative	250 (78)
Reduced intensity	70 (22)
Pretransplantation CMV serostatus, n (%)	
CMV-positive recipient	244 (76)
Missing	17 (5)
PS, n (%)	
PS 0–1	299 (93)
PS 2–4	21 (6.6)
TNC, $\times 10^8$/kg, median (range)	2.7 (0.54–8.8)

2.2. TLR1 genotyping

Real-time polymerase chain reaction (PCR) genotyping for *TLR*1 was performed using the TaqMan-Allelic discrimination method in the StepOnePlus Real-Time PCR system (Applied Biosystems, Foster City, CA, USA) as described previously [16], and the results were analyzed using the Allelic Discrimination software program (Applied Biosystems). The specific probe designed for SNP rs5743551 (−7202A > G) (product No. C_1180670_30) and TaqMan genotyping master mix were purchased from Applied Biosystems.

2.3. Data management and statistical analysis

Data were collected by the JMDP using a standardized report form. Follow-up reports were submitted at 100 days, 1 year and then annually after transplantation. The pretransplantation cytomegalovirus serostatus was routinely measured only in the recipients. Engraftment was confirmed by an absolute neutrophil count of $>0.5 \times 10^9$/L for at least 3 consecutive days. Acute GVHD developing within the first

Table 2
The results of a univariate analysis regarding the association between *TLR*1 variations and clinical outcomes after transplantation. Underlined and bold results represent $P < 0.05$.

Variable	n	3-year PFS	*P*	3-year OS	*P*	3-year TRM	*P*	3-year relapse	*P*
Recipient TLR1 genotype									
G/G	161	68%		63%		16%		16%	
A/G	128	56%	0.22	62%	1.00	18%	0.57	26%	0.45
A/A	31	43%	0.11	56%	1.00	33%	0.16	24%	0.98
G/G	161	**68%**		63%		16%		16%	
A/G or A/A	159	**53%**	**0.042**	60%	0.44	21%	0.25	26%	0.15
Donor TLR1 genotype									
G/G	167	66%		67%		**13%**		21%	
A/G	119	57%	0.40	54%	0.28	21%	0.14	22%	0.76
A/A	34	54%	0.44	56%	0.64	**35%**	**0.0058**	11%	0.24
G/G	167	66%		67%		**13%**		21%	
A/G or A/A	153	56%	0.093	56%	0.081	**25%**	**0.015**	20%	0.69

Variable	n	Grades 2–4 acute GVHD	*P*	Grades 3–4 acute GVHD	*P*	Chronic GVHD	*P*
Recipient TLR1 genotype							
G/G	161	31%		10%		39%	
A/G	128	36%	0.61	5%	0.31	27%	0.21
A/A	31	22%	0.61	3%	0.46	34%	1.00
G/G	161	31%		10%		39%	
A/G or A/A	159	34%	0.70	4%	0.060	29%	0.082
Donor TLR1 genotype							
G/G	167	28%		5%		32%	
A/G	119	36%	0.38	8%	0.58	35%	1.00
A/A	34	43%	0.37	11%	0.53	37%	1.00
G/G	167	28%		5%		32%	
A/G or A/A	153	38%	0.099	9%	0.18	35%	0.46

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