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The recipient CXCL10 +1642C>G variation predicts survival outcomes after HLA fully matched unrelated bone marrow transplantation☆,☆☆

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Abstract CXCL10 is a chemoattractant for immune cells that is involved in several immune-inflammatory disorders. This study retrospectively examined the impact of a single nucleotide variation (rs3921, +1642C>G) in the CXCL10 gene on transplant outcomes in a cohort of 652 patients who underwent unrelated HLA-matched bone marrow transplantation (BMT) for hematologic malignancies. The recipient C/G or G/G genotype was found to be associated with a

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significantly better 5-year overall survival (OS) rate and a lower transplant-related mortality (TRM) rate than the recipient C/C genotype. The recipient C/G or G/G genotype also predicted a reduced incidence of death due to organ failure. The multivariate analysis showed the recipient C/G or G/G genotype to exhibit statistical trends toward beneficial effects on OS but not on TRM. CXCL10 genotyping could therefore be useful in predicting prognoses and creating therapeutic strategies for improving the final outcomes of patients who undergo allogeneic BMT.

1. Introduction

C-X-C motif chemokine 10 (CXCL10), also known as interferon-γ-inducible protein 10, is a chemoattractant for various immune cells such as activated type 1 T helper (Th1) cells, natural killer (NK) cells, dendritic cells (DCs), γδ T cells and macrophages and critically regulates immune-inflammatory responses against microbes and cancer [1,2]. CXCL10 also plays pivotal roles in the initiation and progression of chronic inflammation, autoimmune diseases and allograft rejection [2–8]. A single nucleotide variation in the 3′-untranslated region (3′UTR) of the CXCL10 gene, rs3921 (+1642C>G), is associated with the development of invasive aspergillosis after allogeneic hematopoietic stem-cell transplantation (HSCT) [9] and the disease progression of multiple sclerosis [10] in European populations. The +11 101C>T (rs1554013) and +908A>G (rs4859588) variations in the CXCL10 gene, which also has been reported to correlate with invasive aspergillosis after HSCT, are at a near-perfect disequilibrium with the +1642C>G variation [9]. The role of CXCL10 in anti-infection and anti-tumor immunity and the association between the CXCL10 variant and autoimmunity prompted us to investigate the impact of donor and recipient +1642C>G variation in the CXCL10 gene on the clinical outcomes of patients who undergo allogeneic bone marrow transplantation (BMT) using HLA allele-matched unrelated donors through the Japan Marrow Donor Program (JMDP). The data showed that the recipient C/G or G/G genotype is associated with a significantly better survival rate in patients with hematologic malignancies.

Table 1 Donor and recipient characteristics (first table).

Variable	No.	Ratio
No. of cases	652	
Recipient age, years		
Median	35	
Range	1–67	
Donor age, years		
Median	34	
Range	20–57	
Year of transplant		
Median	2001	
Range	1993–2007	
Recipient CXCL10 genotype		
C/C	562	86%
C/G	85	13%
G/G	5	1%
Donor CXCL10 genotype		
C/C	569	87%
C/G	81	12%
G/G	2	<1%
Recipient sex		
Male	390	60%
Female	262	40%
Donor sex		
Male	410	63%
Female	241	37%
Donor/recipient sex		
Sex matched	419	64%
Female/male	106	16%
Male/female	126	19%
Missing	1	0%

Table 2 Donor and recipient characteristics (second table)
Abbreviation: TNC: total nucleated cell count harvested.

Variable	No.	Ratio
Disease		
Acute myeloid leukemia	208	32%
Acute lymphoblastic leukemia	161	25%
Myelodysplastic syndrome	87	13%
Malignant lymphoma	74	11%
Chronic myeloid leukemia	118	18%
Multiple myeloma	4	1%
Disease stage		
Standard-risk	397	61%
High-risk	255	39%
ABO matching		
Major or/and minor mismatch	252	39%
Major mismatch	143	22%
Minor mismatch	127	19%
Bidirectional	18	3%
Missing	9	1%
Conditioning regimen		
Myeloablative	572	88%
Reduced intensity	80	12%
With total body irradiation	515	79%
Pretransplant CMV serostatus		
CMV positive recipient	444	68%
Missing	70	12%
GVHD prophylaxis		
With cyclosporine	373	57%
With tacrolimus	277	42%
Missing	2	0%
TNC, $\times 10^8$ per kg		
Median	5.1	
Range	0.1–87.0	