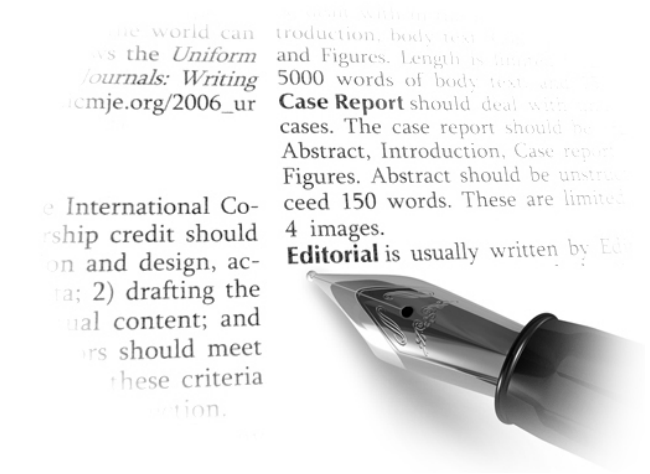

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Editorial

Shedding a new light on the HLA matching

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The first human bone marrow transplantation in a patient with hematologic malignancy took place in the 1950s, but only transient engraftment of the bone marrow was noted [1]. In the 1960s, additional information regarding the HLA system became available; the serologic HLA typing method was developed; and bone marrow transplantations for children with immnunodeficiency were successfully performed [2]. Hematopoietic stem cell transplantation (HSCT) has now become an established and potentially curative treatment modality for many malignant and nonmalignant diseases affecting the hematopoietic and immune systems. However, only approximately 30% of the patients requiring HSCT have an HLA-matched sibling donor; the remaining 70% need to find alternative sources of hematopoietic stem cells (HSCs), such as an HLA-mismatched related donor, a closely HLA-matched unrelated donor (URD), or umbilical cord blood.

The alloantigens differing between donors and recipients become targets for T-cell recognition. Hence, large numbers of genetic differences between donors and recipients increase the risk of both graft rejection and graft-versus-host disease (GVHD); the graft-versus-tumor effect may be beneficial. Therefore, the most important determinant of successful allogeneic HSCT is the degree of HLA matching between the donor and recipient. HLAs are alloantigens and cell surface molecules encoded by class I (HLA-A, HLA-B, and HLA-C) and class II (HLA-DR, HLA-DP, and HLA-DQ) genes, which are a series of closely linked loci known as the major histocompatibility complex (MHC) that are located on chromosome 6 (6p21.3) in humans [3].

Historically, HLA typing was conducted by serologic testing by using antiserum in complement-dependent cytotoxic assays. Recently, more precise DNA-based HLA typing methods using molecular techniques, such as sequence-specific oligonucleotide probe hybridization, sequence-specific primer amplification, sequencing-based typing, and reference strand-based conformation analysis, have been developed and are frequently used. HLA are highly polymorphic, and gene sequencing analysis has revealed more than 800 HLA alleles. The current standard is HLA typing at the HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 genetic loci. An HSCT donor is referred to as a "10/10 allele match" or "perfect match" when both HLA alleles are identical at each of the HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci. While searching for an unrelated donor, high-resolution (4-digit) genetic typing of both the patient and the donor is necessary [4, 5].

In cases of perfect match, minor histocompatibility antigens, which are naturally processed peptides derived from normal cellular proteins, may evoke a strong MHC-restricted response because of the presence of different polymorphisms in the donor and in the recipient. Natural killer (NK) cells may also contribute to alloreactivity, particularly in haploidentical HSCT, through an interaction between killer immunoglobulin-like receptors (KIRs) on NK cells and HLA class I alleles (particularly HLA-C) on mismatched cells [3].

Many retrospective studies have been done to analyze the effects of HLA mismatches (Mms) in adult patients who had undergone URD HSCT in different countries [5-8]. Crocchiolo et al. [6] reported that Mms patients with 9/10 allele match showed a significantly higher risk of mortality, graft failure, and acute GVHD (aGVHD) than patients with 10/10 allele match. Hauzenberger et al. [5] showed that patients with HLA class I allele Mms had high risk of aGVHD and transplant-related mortality (TRM), but HLA class II allele Mms were associated with improved survival. Weisdorf et al. [7] observed significantly worse survival

rates in URD HSCT patients at any matching level, and did not observe augmented graft-versus-leukemia (GVL) effects in Mm URD HSCT patients. However, Kawase et al. [8] reported that, particularly in CML patients, donor-recipient pairs with combinations of HLA-DPB1 were associated with a significantly reduced risk of relapse and better overall survival than completely matched donor-recipient pairs because of the GVL effects.

In this issue of the **Korean Journal of Hematology**, Park et al. [9] report the impact of HLA matching on the outcome of URD HSCT in Korean children. This was the first large, multicenter study to define the relationship between HLA typing and disease outcomes in Korean children who had undergone URD HSCT. Park et al. retrospectively analyzed a large group of patients (N=142, including 109 patients with hematologic malignancies and 33 patients with non-malignant diseases; all the patients belonged to the pediatric age group [≤18 years old]) who had undergone URD HSCT, and all HSC donors and patients were fully typed for HLA-A, HLA-B, HLA-C, and HLA-DR by using high-resolution molecular typing (4-digit level). Park et al. suggested that increased numbers of HLA Mms were associated with reduced overall survival, increased risk of grade III-IV aGVHD, and greater TRM risk, thus confirming the results of many other studies [5-7]. Other important observations included that a single locus Mm at HLA-B or HLA-C was associated with significantly lower survival compared to the survival of patients with 8/8 allele match or a single Mm at HLA-A or DR; these results vary in American and Japanese reports. A single locus Mm at HLA-A showed significant association with high risk of grade III-IV aGVHD, and a single locus Mm at HLA-B showed significant association with high risk of TRM [9]. In their study, Park et al. clearly showed that the disparity in HLA class I, regardless of antigen or allele Mm, had significant negative impacts on the outcome of URD HSCT and was associated with poor survival and high risk of GVHD and TRM. Their study also provided useful information regarding the impact of a specific single HLA locus Mm on disease outcomes in Korean children. This information will be important while choosing optimal HSC donors and improving treatment outcomes of URD HSCT in Korean children with malignant and non-malignant diseases.

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