Editorial

Factors for unrelated donor selection in hematopoietic stem cell transplantation

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Introduction

Allogeneic hematopoietic cell transplantation (allogeneic HCT) is a widely accepted treatment for hematologic malignancies and non-malignant hematologic disorders. The most suitable hematopoietic stem cell donor is a sibling whose human leukocyte antigen (HLA) matches that of the patient (HLA-matched related donor; MRD).[1] However, the chance of finding an HLA-matched sibling donor is only about 25%. In smaller families with fewer children, this likelihood decreases even further.[2] Therefore, to increase the chances of finding a suitable hematopoietic stem cell donor, unrelated hematopoietic cell transplantation (unrelated HCT) has become one of the alternative treatment options.

Graft-versus-host disease (GVHD) is a major complication of hematopoietic cell transplantation. For the past 40 years, the most commonly used regimen to prevent GVHD (the conventional regimen) has been a combination of a calcineurin inhibitor and methotrexate. However, recent studies have shown that the use of post-transplant cyclophosphamide (PTCy) in patients undergoing unrelated HCT with matched unrelated donors (MUD) results in better transplantation outcomes compared to the conventional regimen.[3] Last year, the European Society for Blood and Marrow Transplantation (EBMT) published a recommendation stating that PTCy or rabbit anti-thymocyte globulin should be considered standard agents for GVHD prophylaxis when peripheral blood stem cells are used in unrelated HCT.[4] The use of PTCy for GVHD prophylaxis has shown favorable outcomes in patients receiving transplants from HLA-mismatched donors, particularly haploidentical donors. This has led to the consideration of using PTCy for GVHD prevention in unrelated HCT with HLA-mismatched unrelated donors (MMUD). In such cases, the impact of HLA mismatch on transplant outcomes may differ from that seen with the conventional GVHD prophylaxis regimen. Therefore, the factors involved in selecting an unrelated donor may vary depending on the prophylactic regimen used. This article will discuss the various factors that influence unrelated donor selection in the context of both conventional regimens and PTCy-based GVHD prophylaxis.

HLA factors

1. Level of HLA matching

HLA mismatch is a critically important factor in unrelated HCT when using a conventional regimen for GVHD prophylaxis. Mismatches at the HLA-A, -B, -C, and -DRB1 loci are associated with decreased survival rates, and the decline in survival correlates with the increasing number of HLA mismatches. However, there is no significant difference in survival outcomes between antigen-level mismatches and allele-level mismatches.[5,6] Guidelines from the National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR)[7] recommend that an 8/8 HLA-MUD should be prioritized over a 7/8 MMUD for transplantation.

In cases of unrelated HCT using PTCy for GVHD prophylaxis, several studies have reported that HLA

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mismatch is not associated with hematopoietic stem cell transplant outcomes.[8,9] A single-center study of 144 patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) who received PTCy found that the 1-year overall survival rates did not differ between patients who underwent unrelated HCT from 7/8 MMUD and those from donors with less than 7/8 HLA match.[8] A multicenter study of 1,011 AML patients who received PTCy, using data from the EBMT database, found no significant differences in leukemia-free survival (LFS), acute GVHD, chronic GVHD, non-relapse mortality, relapse incidence, or overall survival between patients who underwent unrelated HCT from 10/10 MUD and those from 9/10 MMUD.[9] However, there are conflicting results regarding the above conclusion. A study involving 1,523 patients with hematologic malignancies who received PTCy and 15,630 patients who did not found that the group receiving unrelated HCT from 9/10 MMUD with PTCy was associated with decreased overall survival; Hazard Ratio (HR) 1.32, 99% confidence interval (CI) 1.04-1.68, $p = 0.003$ compared to those receiving unrelated HCT from 10/10 MUD.[10] When analyzing by HLA mismatch class, HLA class I mismatch was significantly associated with reduced overall survival (HR 1.32, 99% CI 1.02-1.71, $p = 0.006$). The researchers concluded that HLA mismatch, especially HLA class I mismatch, remains an important factor even when PTCy is used for GVHD prophylaxis. Currently, there are no international guidelines recommending the use of HLA mismatch status as a criterion for unrelated donor selection in patients receiving PTCy for GVHD prevention.

2. Donor-specific antibody (DSA)

The guidelines from the NMDP and the CIBMTR[7] state that in unrelated HCT using conventional regimens for GVHD prophylaxis, donors should be selected so that the patient does not have DSA against the mismatched HLA of the donor. This is because the presence of DSA in the patient increases the risk of primary graft failure.

Because antibody-mediated rejection is a major cause of graft failure regardless of donor type or the GVHD prophylaxis regimen used.[11] The recommendation from the American Society of Transplantation and Cellular Therapy (ASTCT), published last year, states that donors who do not have HLA matching the recipient's anti-HLA antibodies should be selected for all types of donors with mismatched HLA.[11] Therefore, although there are currently no international guidelines specifically addressing DSA in the selection of unrelated donors when PTCy is used for GVHD prophylaxis, it can be reasonably inferred that donors whose mismatched HLA do not correspond to the patient's DSA should be preferred to minimize the risk of primary graft failure.

3. HLA-B leader

HLA-B leader refers to the amino acid at position -21, which is encoded by exon 1 of the HLA-B gene. This amino acid exhibits dimorphism, being either methionine (M) or threonine (T). It plays a crucial role in binding to HLA-E and regulating the natural killer (NK) cell response through the inhibitory NKG2A receptor.[12] Petersdorf and colleagues studied 33,982 patients who underwent unrelated HCT using conventional GVHD prophylaxis regimens and found that B-leader matching was associated with a reduced risk of acute GVHD.[13] Therefore, selecting donors with matching B-leader types to the patient may be beneficial for better outcomes. However, the significance of B-leader matching in unrelated HCT using PTCy remains unclear due to insufficient current research data.

4. HLA-DPB1 matching

The consideration of HLA-DPB1 matching involves classifying HLA-DPB1 alleles based on alloreactive T-cell responses, which can be grouped into three T-cell epitope (TCE) categories according to their immunogenic potential: high, intermediate, and low.[14,15] An HLA-DPB1 allele mismatch within the same TCE group is defined as a "permissive mismatch", whereas a mismatch between alleles belonging to different TCE groups is defined as a "non-permissive mismatch". Studies in patients

undergoing unrelated HCT using conventional regimens for GVHD prophylaxis have shown that non-permissive HLA-DPB1 mismatches are associated with decreased overall survival compared to patients receiving DPB1-matched donors. In contrast, overall survival does not differ significantly between patients with permissive DPB1 mismatches and those with DPB1 matches.[14,16] Guidelines from NMDP/CIBMTR[7] recommend avoiding donors with non-permissive mismatches and preferentially selecting those with DPB1 matches or permissive mismatches. However, the impact of HLA-DPB1 matching in unrelated HCT using PTCy for GVHD prophylaxis remains unclear due to limited data.

Non-HLA factors

1. Donor age

Donor age is a clearly important factor in unrelated HCT using conventional regimens for GVHD prophylaxis, supported by multiple studies.[17-19] Accordingly, the NMDP/CIBMTR guidelines[7] recommend selecting younger donors over older donors in this setting. For unrelated HCT using PTCy for GVHD prophylaxis, there are currently no international guideline recommendations regarding donor age. However, several studies have reported the importance of donor age in patients receiving PTCy.[9,20] For example, Sanz, et al. reported that donors over 30 years of age were associated with poorer outcomes, including higher relapse rates and reduced leukemia-free and overall survival, compared to younger donors. They suggested that donor age may be more important than HLA matching when selecting unrelated donors for GVHD prophylaxis with PTCy.[9] Additionally, a study by the Acute Leukemia Working Party (ALWP) of the EBMT[20] showed that patients receiving unrelated HCT from MMUD younger than 35 years had lower rates of acute GVHD and non-relapse mortality compared to those receiving haploidentical transplants from donors older than 35 years. In summary, donor age is an important consideration in unrelated HCT both when using conventional regimens and PTCy for GVHD prophylaxis.

In cases where multiple donors are available and both donor age and HLA-DPB1 matching need to be considered, which factor should be prioritized? For example, between a younger donor with a non-permissive DPB1 mismatch and an older donor with a permissive mismatch, which donor is more suitable? A study of 10,783 patients who received 10/10 HLA-matched unrelated HCT with conventional GVHD prophylaxis[21] found that patients receiving grafts from younger donors with non-permissive DPB1 mismatch had higher overall survival than those receiving grafts from older donors with permissive mismatch. Additionally, patients receiving transplants from older donors (> 35years) had similarly increased mortality risks regardless of permissive or non-permissive DPB1 mismatch.

2. Cytomegalovirus (CMV) serostatus

The NMDP/CIBMTR[7] guidelines do not consider donor CMV serostatus a factor in selecting unrelated donors for patients receiving conventional GVHD prophylaxis, as studies have found no significant association between donor CMV serostatus and transplant outcomes.[19] In unrelated HCT using PTCy for GVHD prophylaxis, regardless of donor or recipient CMV serostatus, PTCy is associated with an increased risk of CMV infection.[22] Therefore, patients receiving PTCy for GVHD prevention should receive proactive CMV infection prophylaxis.

3. ABO compatibility

Although some studies have reported that both minor and major ABO mismatches between patients and unrelated donors are associated with decreased overall survival after HCT,[23,24] a large-scale study involving 11,039 patients found no statistically significant impact of ABO mismatch on patient survival.[19] Therefore, the NMDP/CIBMTR[7] guidelines do not include ABO compatibility as a criterion for unrelated donor selection in patients receiving conventional GVHD prophylaxis. Currently, data on the impact of ABO mismatch in unrelated HCT using PTCy for GVHD prophylaxis remain limited.

Conclusion

In summary, an HLA-matched related donor (MRD) remains the preferred choice for allogeneic HCT. For patients without a suitable MRD, unrelated donors offer a valuable alternative to expand treatment options. The use of PTCy for GVHD prophylaxis has become increasingly common, and donor selection criteria may differ from those used with conventional regimens. Notably, the impact of HLA mismatching may be reduced with PTCy. However, DSAs and donor age continue to influence outcomes in unrelated HCT, regardless of the GVHD prophylaxis strategy. The relevance of other donor factors warrants further investigation.

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