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Which factors influence the development of GVHD in HLA-matched or mismatched transplants?

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Abstract

The sheer diversity of HLA alleles makes the probability of finding matched unrelated donors for patients requiring hematopoietic cell transplantation (HCT) a complex situation. New evidence suggests that mismatching at certain HLA loci may provide a greater benefit in terms of graft-versus-leukemia effect than other mismatches when HLA-matched donors are not available. This review summarizes the current understanding of HLA matching requirements for unrelated donor HCT.

Keywords

allele; GVHD; graft-versus-host disease; GVL; graft versus leukemia; hematopoietic cell transplantation; HCT; HLA; matched; mismatched

Introduction

Consideration of both HLA and non-HLA factors when selecting the optimal allogeneic donor may optimize clinical outcome for patients undergoing hematopoietic cell transplantation (HCT). The current state-of-the-art is based on matching donor HLA-A, C, B, DRB1, and DQB1 alleles if possible (Table 1); however, consideration for additional loci within the major histocompatibility complex (MHC) is actively being investigated in the research arena. When HLA-matched donors are not available, there is new evidence to suggest that mismatching at certain HLA loci may provide a greater graft-versus-leukemia effect than others. In this review, the current understanding of HLA matching requirements for unrelated donor HCT is summarized.

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Patient-donor matching

There are ample clinical data that demonstrate the benefit of patient-donor matching of HLA determinants to lower risks of acute and chronic graft-versus-host disease (GVHD) and to improve survival. The probability of finding HLA-matched unrelated donors is made complex by the sheer diversity of HLA alleles [1]. With over 27 million unrelated donors worldwide, the probability that any given patient may identify an HLA-matched donor depends on the specific HLA haplotypes and the size and composition of the donor registries [2,3].

When more than one HLA-matched unrelated donor is available, non-HLA donor characteristics provide an important additional selection feature [4]. In a retrospective analysis of over 10,000 transplants, donor HLA matching was confirmed to be an important risk factor for the development of acute GVHD and overall survival. Donor age was an important variable for survival. Female donors with a history of at least one pregnancy were associated with higher risk of chronic GVHD. Additional patient features include patient age, CMV serostatus, performance score, and disease diagnosis, all of which influence survival after transplantation [4].

New information on HLA-DRB3, DRB4, DRB5 and MICA genes within the MHC provides an additional level of selection among HLA-A, C, B, DRB1, DQB1-matched unrelated donors. Low-expression gene products of HLA-DRB3, DRB4, and DRB5 contribute to increased risks when accompanied by mismatching at HLA-A, B and/or DRB1, but not in otherwise fully HLA 10/10-matched transplantation [5]. These results suggest that when HLA-A, B, C, DRB1 or DQB1-mismatched donors are available, additional testing of DRB3/4/5 may help to lower risks. Most recently, mismatching for the non-classical class I gene, MICA, has been shown to impact GVHD and survival in some [6,7], but not other, studies [8].

Historically, limiting the total number of HLA mismatches is associated with better outcome; however, not every mismatch that increases GVHD lowers relapse risk [9]. HLA-A, B, C, DRB1, DQB1 and HLA-DPB1 disparity each increase the risk of grades III/IV acute GVHD, but only mismatching at HLA-C and DPB1 are associated with lower relapse [9]. Biological mechanisms for HLA-C and DPB1-associated risks may include the level of surface expression of these molecules. Risks of GVHD and non-relapse mortality are lower when the patient’s HLA-C and HLA-DPB1 mismatches are expressed at lower than at higher levels [10,11].

Although historical outcomes data on the impact of HLA disparity and clinical outcome were based on the use of myeloablative conditioning and bone marrow as the stem cell source, the negative effects of HLA mismatching are evident with the use of peripheral blood stem cell products and after reduced-intensity conditioning regimens (Table 2) [12,13].

Cord blood and haploidentical transplants

Do the same principles of HLA matching in unrelated donor transplantation also pertain to cord blood and haploidentical transplantation? Emerging evidence suggests that HLA disparity is associated with higher risk of transplant-related mortality in cord blood transplantation compared to matching [14]. With the use of post-transplantation cyclophosphamide in haploidentical transplantation, the deleterious effects of HLA mismatching on the non-shared haplotype are attenuated (Table 2) [15].

In conclusion, both HLA and non-HLA factors influence the risks of GVHD and mortality after unrelated donor transplantation. Future research into the features that define permissive mismatches will enable more patients to benefit from transplantation without increasing post-transplant risks.

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Table 1

State-of-the-Art 2017: HLA Matching in Support of Allogeneic Hematopoietic Cell Transplantation

- Match if possible
  - When more than 1 matched donor is available: consider non-HLA donor characteristics (eg, avoid female donors with ≥ 1 pregnancy)
  - Consider additional loci: HLA-DRB3/4/5 and possibly MICA
- When matched donors are not available
  - Limit the total number of HLA mismatches
  - Consider mismatching against 1 low-expression HLA-C or HLA-DPB1 recipient allotype: lower risk of GVHD but GVLE

Table 2

Summary of HLA Criteria for Donor Selection.

Unrelated Donor BM	Unrelated Donor PBSC	Haploidentical Donor	Cord Blood Unit(s)
1 Restrict to 1 HLA-A, B, C or DRB1	**1** Restrict to 1 HLA-A, B, C or DRB1	**1** NMA HCT with BM and post-HCT CY: overcomes HLA mismatching	**1** HLA-A, B low/ DRB1 high resolution typing
2 Isolated DQB1 might be tolerable	**2** Isolated DQB1 might be tolerable	**2** KIRs may promote anti-leukemic activity	**2** Consider HLA-C (↑ engraftment and ↓ NRM)
3 Avoid DQB1 + other mismatch	**3** Avoid DQB1 + other mismatch		**3** Select better matched units with high cell dose
	4 RIC: 1 HLA mismatch is high risk		

BM, bone marrow

PBSC, peripheral blood stem cells

RIC, reduced intensity conditioning

NMA, non-myeloablative conditioning

HCT, hematopoietic cell transplantation

CY, cyclophosphamide

KIR, killer immunoglobulin receptor

NRM, non-relapse mortality