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Simulation of non-inherited maternal antigens acceptable HLA mismatches to increase the chance of matched cord blood units: Hong Kong's experience

Janette Kwok[a,*], Mengbiao Guo[b,*], Wanling Yang[b], Patrick Ip[b], C.K. Lee[c], Liwei Lu[d], Godfrey C.F. Chan[b], Derek Middleton[e], Henk G.M. van der Zanden[f]

[a] Division of Transplantation and Immunogenetics, Queen Mary Hospital, Hong Kong
[b] Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong
[c] Hong Kong Red Cross Blood Transfusion Services, Hong Kong
[d] Department of Pathology, The University of Hong Kong, Hong Kong
[e] Transplant Immunology, Royal Liverpool Hospital, Liverpool, UK
[f] Matchis Foundation, Leiden, Netherlands

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ABSTRACT

In Cord blood transplantation (CBT), the non-inherited maternal antigen (NIMA) virtual six HLA matched CB is found to have similar outcomes to six HLA inherited matched CB. Such virtual HLA matched CB units can be generated by substituting the inherited alleles with one to three NIMAs. In Hong Kong Cord Blood Bank, CB units have no NIMA defined. 100 CB samples were collected with NIMA defined. Retrospective searches of Hong Kong patients (n = 520) were matched against the inherited and virtual HLA phenotypes of NIMA CB file. One to three NIMA matches was analyzed, virtual six HLA matches were identified for 31.7% patients, 29.4% from CB units with 5/6 HLA match with 1 NIMA match and 1.7% CB units with a 4/6 HLA match and 2 NIMA matches. However, searches in the 167,201 Bone Marrow Donors Worldwide CB units with defined NIMA did not yield similar increases, possibly due to the ethnicity differences between populations. The match performance rises from 26% to 60% after including the NIMA match. Comparing the match performance of 32% in a previous Dutch study, we calculated with 60% matching in this smaller size study. This provides a solid ground to considering NIMA in stem cell donor selection which was adopted in some centers, to be extended to Asian and local CB registries to increase the chance for matches and also to improve patient outcomes, increase the utilization of CB units, enhance clinical flexibility and signify economic intelligence.

1. Introduction

Human leukocyte antigens (HLA) matched hematopoietic stem cell transplantation (HSCT) is the ultimate treatment for most hematological malignancies. However, many patients fail to find a suitable matched donor. By using HLA-matched cord blood transplantation (CBT), the donor pool can be increased.

Transplant-related mortality (TRM) and acute graft versus host disease (GVHD) remain a challenge following HLA-mismatched CBT [1,2]. However, many patients have to accept an HLA-mismatched cord blood (CB) unit because of the lack of a 6/6 HLA match (HLA-A and -B at intermediate resolution level and -DRB1 at high resolution level), particularly for patients of Chinese ethnicities [3] despite of the listing of more than 700,000 unrelated CB units on the Bone Marrow Donors Worldwide (BMDW) [4]. Alternate HLA-matching strategies are clinically desired.

Non-inherited maternal antigens (NIMA) are defined as protein products that the mothers express but not the offspring [5]. During normal pregnancy, a bidirectional regulation happens such that the maternal immune system tolerates the inherited paternal antigens (IPA) expressed by the fetus while the developing fetal immune system tolerates NIMA. The production of T cytotoxic cells specific for NIMA HLA-restricted minor histocompatibility antigens, controlled by T regulatory cells was noted in the immune system of a 4-month-old human fetus and these T cytotoxic cells can be detected in fetal blood, cord blood, and adult peripheral blood [6–8]. However, this immunological consequences of fetal exposure in the CB to maternal cells was not yet included in the existing CB unit selection for HSCT [9]. It selects the CB unit with the highest total nucleated cell (TNC) dose among the best HLA-matched donor available, i.e. 4/6 or better for HLA-A and -B at intermediate resolution level and -DRB1 at high resolution level. In the retrospective study done by Van Rood et al, patients with CBT from 5/6

* Corresponding authors at: Division of Transplantation and Immunogenetics, Department of Pathology, Queen Mary Hospital, Pokfulam Road, Hong Kong (J. Kwok).
E-mail addresses: kwoksy@ha.org.hk (J. Kwok), andyk2@connect.hku.hk (M. Guo).

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Table 1
Virtual HLA Genotypes created from NIMA.

Cord blood (CB)	A11, A24; B46, B7; DRB1*07:01, DRB1*09:01	
Mother of the CB	A11, **A2**; B46, **B13**; **DRB1*03:01**, DRB1*09:01	NIMA = A2, B13 and DRB1*03:01

Combining the CB genotype with the NIMA A2, B13 and DRB1*03:01 creates the following virtual CB genotypes for HLA -A, B, DRB1:

One substitution	**Two substitutions**	**Three substitutions**
A11, **A2**; B46, B7; DRB1*07:01, DRB1*09:01	A11, A24; **B13**, B7; **DRB1*03:01**, DRB1*09:01	A11, **A2**; **B13**, B7; **DRB1*03:01**, DRB1*09:01
A2, A24; B46, B7; DRB1*07:01, DRB1*09:01	A11, A24; B13, B7; **DRB1*03:01**, DRB1*07:01	A11, **A2**; **B13**, B7; **DRB1*03:01**, DRB1*07:01
A11, A24; B46, **B13**; DRB1*07:01, DRB1*09:01	A11, A24; B46, **B13; DRB1*03:01**, DRB1*09:01	**A2**, A24; **B13**, B7; **DRB1*03:01**, DRB1*09:01
A11, A24; **B13**, B7; DRB1*07:01, DRB1*09:01	A11, A24; B46, **B13**; **DRB1*03:01**, DRB1*07:01	**A2**, A24; **B13**, B7; **DRB1*03:01**, DRB1*07:01
A11, A24; B46, B7; **DRB1*03:01**, DRB1*09:01	A11, **A2**; B46, B7; **DRB1*03:01**, DRB1*09:01	A11, **A2**; B46, **B13**; **DRB1*03:01**, DRB1*09:01
A11, A24; B46, B7; DRB1*07:01, **DRB1*03:01**	**A2**, A24; B46, B7; **DRB1*03:01**, DRB1*09:01	A11, **A2**; B46, **B13**; **DRB1*03:01**, DRB1*07:01
	A11, **A2**; B46, B7; **DRB1*03:01**, DRB1*07:01	**A2**, A24; B46, **B13**; **DRB1*03:01**, DRB1*09:01
	A2, A24; B46, B7; **DRB1*03:01**, DRB1*07:01	**A2**, A24; B46, **B13**; **DRB1*03:01**, DRB1*07:01
	A11, **A2**; **B13**, B7; DRB1*07:01, DRB1*09:01	
	A11, **A2**; B46, **B13**; DRB1*07:01, DRB1*09:01	
	A2, A24; **B13**, B7; DRB1*07:01, DRB1*09:01	
	A2, A24; B46, **B13**; DRB1*07:01, DRB1*09:01	

Bold text facilitates the understanding that two HLA genotypes combined deliver 26 different HLA genotypes.

HLA antigen matched/1 NIMA-matched donors (6/6 virtual match) and even from those with 4/6 HLA antigen matched/ 1 NIMA matched donors (5/6 virtual match), have significantly less TRM, associated with improved neutrophil recovery and probably reduced incidence of relapse (P = 0.07) [10]. Similar findings were also confirmed by a Eurocord-Center for the International Blood and Marrow Transplant Research study [11].

Taking into consideration of the better outcomes with NIMA matched CBT in these studies, NIMA could prospectively be considered during CB unit selection if the maternal HLA of the corresponding CB unit is known. CB transplantation accounts for around 2.5% of the worldwide stem cell donor pool but contributes about 20% of all unrelated HSCT [12]. Routine maternal HLA typing of stored CB units could provide patients who otherwise would receive HLA-mismatched CB units with 6/6 virtual matched CB units and improve the clinical outcomes.

A recent study demonstrated that by substitution of 1, 2 or 3 of the CB inherited HLA-A, -B and/or -DRB1 alleles for a NIMA can yield 26 possible “virtual phenotypes”. This can considerably increase the potential number of phenotypes accessible for donor searches [13]. Another retrospective study that evaluated the availability of a NIMA matched CB units with sufficient TNC dose for European Caucasoid and other ethnicities from both the British Bone Marrow Registry (BBMR) and the BMDW registry [14].

If 4–5/6 HLA matches and 1 NIMA match improved TRM and neutrophil recovery, it could be anticipated that 4/6 HLA matches and 2 NIMA matches would give similar advance. Previous studies have shown improved outcomes of NIMA-matched haplo-identical sibling renal and stem cell transplantations, suggesting that unrelated 3 HLA antigen mismatched CB units compensated by 3 NIMA matches could also provide improved survival [15,16]. Unfortunately, such prospective studies with 3–4/6 HLA-matched CB units compensated by 2 and 3 NIMA matches are yet to be performed. Nonetheless, including them in the corresponding calculations would permit an enriched and complete picture of the impending efficacy of NIMA matching. Therefore, we have calculated by adding such phenotypes, denoting the results from CBT with 3–5/6 HLA matches compensated by 1–3 NIMA matches.

2. Materials, methods, and study designs

2.1. Patient and donor files

Our study included a patient file of 520 Hong Kong patients in which 120 are pediatric and 400 are adults, of Chinese in ethnicity, with the required HLA typing level, needing unrelated HSCT between 2014 and 2016. We used the following HLA-typed CBU files: file 1, NIMA file (NIMA CBU) of 100 units, whose maternal HLA genotypes and, hence, their NIMA, are known; file 2, a Hong Kong CBU file (HK CBU) (n = 3892 units); and file 3, the BMDW file, limited to the CB units with the required level of HLA typing and the required mother types (n = 167,201 of 465,000 units). The sample of 100 mother typed in file 1 is aimed to obtain NIMA only for quantifying the Increase of HLA genotypes by Creating Virtual phenotypes.

2.2. HLA typing

CB unit and maternal blood were HLA typed at the intermediate level resolution for HLA-A and B loci and for DRB1 loci at high resolution level at the standard requirement of CB unit matching.

2.3. Simulated CB donor searches

Searches for inherited HLA matched at 6/6 (0 mismatch), 5/6 (1 mismatch) and 4/6 (2 mismatches) level and virtual HLA matched at 6/6 (1–3 NIMA) were done on the NIMA CBU file and BMDW registries. At the time of investigational search, 100 NIMA CB units and 167,201 BMDW listed CB units had maternal HLA typing available. Only CB units meeting the prerequisite HLA matching were counted as potential donors. The BMDW CBU Match Program was also searched for inherited HLA matched CB units by selecting the functions of “identical and one allele/Ag mismatch” and “two Ag/allele mismatches”.

Each donor-recipient HLA mismatch matched to the donor NIMA were assigned as a NIMA virtual 6/6 match. These comprised of 5/6 + 1 NIMA, 4/6 + 2 NIMA and 3/6 + 3 NIMA matches. NIMA matches were identified using the BMDW NIMA Match Program by selecting the functions of “identical matches” and “include 2 and 3 NIMA in match”.

Search for inherited 6/6 HLA matches were selected first. Patients with no matched donor were then examined for NIMA match. Patients were assessed for a 3–5/6 inherited HLA match and NIMA match.

2.4. Virtual and real genotype illustration

Table 1 illustrates a model example. The genotype of CB unit for the HLA-A loci is A11, A24 and the mother’s type of the CB unit is A11, A2. Replacing inherited paternal HLA-A24 by the NIMA HLA-A2 creates the (virtual) phenotype HLA-A11, A2. In addition, by substituting the NIMA HLA-A2 for the inherited maternal HLA-A11 creates the (second virtual) genotype HLA-A2, A24. Similar NIMA substitutions at the HLA-B