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Post-transplantation cyclophosphamide-based graft-versus-host disease prophylaxis in a patient transplanted from a matched related but non-sibling donor

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ABSTRACT

While post-transplantation cyclophosphamide (PTCy)-based prophylaxis of graft-versus-host disease (GVHD) was increasingly used not only in haploidentical transplantation but also in transplantation from matched related donors, its benefit in the setting of matched non-sibling donors (MNSD) had not been discussed or reported. A 70-year-old Japanese male who was diagnosed with acute myeloid leukemia with internal-tandem duplication of the *FLT3* gene was treated with intensive chemotherapy and quizartinib. After one cycle of consolidation, he was transplanted from an HLA 8/8 matched daughter. GVHD prophylaxis consisted of PTCy, tacrolimus, and mycophenolate mofetil. Neutrophil engraftment was attained at day 16, and he was still in remission at 1 year without complication, but except or grade II acute skin GVHD. Although there had been few reports on PTCy-based GVHD prophylaxis in transplantation from MNSD, our report suggested that these patients could benefit from this type of GVHD prophylaxis.

Keywords: Acute myeloid leukemia; Matched non-sibling donor; Allogeneic transplantation; Post-transplantation cyclophosphamide; Graft-versus-host disease.

INTRODUCTION

Allogeneic transplantation was still an indispensable procedure for the treatment of hematologic disorders, and selecting a suitable donor was one of the most important parts. While recent studies demonstrated that donor age would have a greater impact on transplant outcome than donor type,[1] transplantation from a matched sibling donor (MSD) was generally accepted as a desirable donor compared with a matched unrelated donor (MUD) or mismatched related/unrelated donors (MMRD/MMUD).[2] However, studies on transplantation from matched non-sibling donors (MNSD) were lacking, probably because of their rarity in many Western countries. Recently, the effectiveness of prophylaxis of graft-versus-host disease (GVHD) using post-transplantation cyclophosphamide (PTCy) has been increasingly reported not only in haploidentical settings but also in transplantation from MSD.[3-6] Here, we report a case with acute myeloid leukemia (AML) transplanted from an HLA-matched daughter using PTCy-based GVHD prophylaxis.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Case presentation

A 70-year-old Japanese male visited a local clinic complaining of dyspnea and was transferred to our hospital, suspected of acute leukemia. The laboratory data at admission were significant for elevated white blood count (17.1×10^9/L) with increased blasts (7%), low hemoglobin level (7.0 g/dL), low platelet count (68×10^9/L), and elevated LDH (275 IU/L). Bone marrow testing revealed proliferation of myeloblasts (28.8% of all nucleated cells), which were positive for myeloperoxidase stain, and genetic analysis for the *FLT3* gene revealed the presence of internal-tandem duplication. A diagnosis of AML with maturation was confirmed, and treatment with idarubicin, cytarabine, and quizartinib was initiated following the protocol of the QuANTUM-First study.[7]

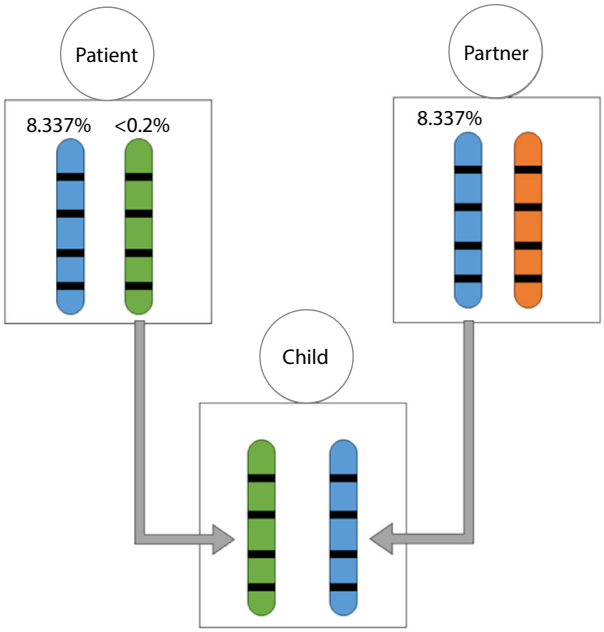
As he was considered eligible for allogeneic transplantation, a search for donors was also performed. He had no siblings but had a healthy daughter. In principle, typing of her HLA might not be necessary, and transplantation from a MUD should be the primary consideration. However, 2 weeks later, he was going to stay in a distant prefecture for 2 months due to work commitments, and it would become difficult to visit the hospital during this period. In case of induction failure and need for immediate haploidentical transplantation, his HLA test was also performed. Contrary to our expectation, his HLA haplotype was matched for HLA-A, B, C, and DRB1 to that of this patient (A*24:02, A*31:01, B*51:01, B*52:01, C*12:02, C*14:02, and DRB1*15:01, DRB1*15:02). HLA typing was performed using Luminex technology, and other loci, including HLA-DPB1 or DQB1, were not investigated.

He attained complete remission after the first induction, and after one course of consolidation with high-dose cytarabine and quizartinib, transplantation from the daughter was performed. Considering the paucity of studies on transplantation from MNSD, the protocol of this transplantation followed the BMT CTN 1703 study,[3] which adopted the same conditioning and GVHD prophylaxis for transplantation from MSD and MUD. In detail, the conditioning regimen consisted of fludarabine (180 mg/m^2) and busulfan (12.8 mg/kg/body), and prophylaxis of GVHD consisted of PTCy, tacrorimus and mycophenolate mofetil (MMF). Neutrophil engraftment was attained at day 16, and quizartinib maintenance was initiated at day 49. Grade II acute skin GVHD occurred at day 56, which was successfully treated with prednisolone. Immunosuppressive drugs were terminated at day 273, and he was still in remission at 1 year.

DISCUSSION

Availability of MNSDs was considered to depend on the frequency of consanguineous marriage,[8] which was prohibited in our country. According to a comprehensive study of Japanese HLA haplotypes, the haplotype of A*24:02–C*12:02–B*52:01–DRB1*15:02 was the most common pattern in Japan, and its frequency was estimated to 8.337%.[9] As the frequency of the other haplotype, A*31:01–C*14:02–B*51:01–DRB1*15:01, was at least less than 0.2%, it would be reasonable to speculate that the partner of the patient had this most frequent allele by chance, and the less frequent allele of the donor was derived from the patient (Fig. 1). One of the limitations of our study was that typing of other loci such as HLA-DPB1 and -DQB1 was not performed. In our country, although increased risks of GVHD by HLA-DPB1 or -DQB1 mismatch were also demonstrated,[10,11] HLA matching was usually assessed based on HLA-A, -B, -C, and -DRB1 only, at least in the setting of related transplantation.[12] As there were complications specific to PTCy-based GVHD prophylaxis, such as hemorrhagic cystitis,[13] it was mandatory to identify who would truly benefit from this type of GVHD prophylaxis, and extended HLA typing should have been performed in our case to assess accurate GVHD risk.

While the benefits of PTCy-based GVHD prophylaxis were increasingly reported outside the haploidentical settings, protocols of prospective studies which directly compared PTCy-based GVHD prophylaxis to traditional prophylaxis, such as the BMT CTN 1703 study, ALLG BM12 CAST trial[4] and a study by Brissot et al.,[5] included only transplantation from MSDs. HOVON 96 trial[6] and BMT CTN 1701 trial[14] used the term "matched related," but the exact number of MSDs and MNSDs was not inferred. As far as we knew, there were only three studies of PTCy in which MNSDs were included and the number of MNSDs was clearly inferred (Table 1).



Source: Elaborated by the authors.

Figure 1. Presumed pattern of HLA haplotypes. The scheme showed the presumed HLA allele status of the family of our patient. Each bar showed each HLA allele, and the haplotype of the blue bar was A*24:02–C*12:02–B*52:01–DRB1*15:02, which was seen in 8.337% of the Japanese population. The haplotype of the green bar was A*31:01–C*14:02–B*51:01–DRB1*15:01, which was seen in less than 0.2%. The orange bar had an unknown haplotype.

Table 1. Previous studies included transplantation from MNSDs, which adopted a PTCy-based protocol as GVHD prophylaxis.

	Kanakry et al.[16,17] Single arm, phase II	**Javier et al.[14] Randomized phase II**	**Leo et al.[15,17] Single arm, phase I/II**
Number of patients	MSD n = 44 MNSD n = 1 UD n = 47	MSD n = 29 MNSD n = 4 UD n = 59	MSD n = 77 MNSD n = 1 UD n = 39
Source	Bone marrow	Peripheral blood stem cells	Bone marrow
Diseases	High-risk malignancies	Various diseases	AML, MDS, ALL, CML
Conditioning	Flu/Bu	Flu/Bu, Flu/Cy, Flu/Mel, Flu/TBI, Flu/Cy/TBI	Bu/Cy
GVHD prophylaxis	PTCy alone	TAC/MMF/PTCy TAC/MTX/Bor TAC/MTX/MVC	PTCy alone

Source: Elaborated by the authors.

In the phase 2 BMT CTN 1203 study, which compared PTCy-based prophylaxis to tacrolimus and MMF with bortezomib or maraviroc, only four patients transplanted from MNSDs received PTCy-based prophylaxis.[15] Two studies on GVHD prophylaxis with PTCy alone included one patient transplanted from an MNSD each.[16-18] Outcomes of these patients were not reported, so the benefit was not clear in this population.

As for our patient, although the benefit of PTCy-based GVHD prophylaxis in MNSD settings was not established, as discussed above, a recently published subgroup analysis of the BMT CTN 1703 study demonstrated that the benefit from PTCy was highest in elderly patients.[19] This study adopted the same GVHD prophylaxis for MSD and matched or 7/8 MMUD, and one study from India indicated that the risk of GVHD of MNSD would

be estimated between MSD and MMRD.[20] Thus, on these grounds, we considered that our patient could fully benefit from PTCy-based GVHD prophylaxis, although it remained to be examined whether the same could be applied to other cases.

It was true that there had been little discussion on whether transplantation from MSD and MNSD should be considered separately, or whether it was acceptable to group MSD and MNSD as MRD, possibly reflecting the rarity of HLA MNSDs in many Western countries. An analysis of the EBMT registry on 2355 patients with non-malignant diseases included only 53 patients (2.3%) transplanted from MNSDs.[21] In eastern Asia, to which our country belonged, a retrospective analysis of 2726 transplants in a large Chinese transplantation center found only 23 MNSD cases (0.8%). Although whether transplantation from MNSDs carried different risks or benefits from transplantation from MSDs was not clear, there had been several studies in which outcomes of transplantation from MNSDs were compared with other donors (Table 2). A study from Saudi Arabia[22] and another study from Iran[23] found no differences between transplantation from MSDs and MNSDs, but the latter study found a significantly lower risk of GVHD compared to MUDs. A retrospective study from Turkey showed similar clinical outcomes among MSDs, MNSDs, and MUDs, but this study was limited to patients with thalassemia.[24] A study from India, which included 81 patients transplanted from MNSDs, showed that the 3-year survival rate of transplantation from MNSDs (54.4%) was between that from MSDs (70.9%) and MMRDs (35.9%).[20] A study from China found a higher mortality rate compared to haploidentical transplantation.[8] As none of these studies adopted PTCy-based GVHD prophylaxis for transplantation from MNSDs, these results strongly suggested that the benefit of PTCy-based GVHD prophylaxis in this type of transplantation should be separately evaluated.

Table 2. Previous studies comparing transplantation from MNSD s with other donors.

Country	Saudi Arabia[9]	India[12]	Turkey[11]	China[6]	Iran[10]
Diseases	Non-malignant diseases	Various diseases, but most were non-malignant (n = 176)	β-thalassemia	AML, ALL, MDS	Fanconi anemia
Number of patients	MSDs n = 46 MNSDs n = 30	MSDs n = 111 MNSDs n = 81 MMRDs n = 34	MSDs n = 18 MNSDs n = 14 MUDs n = 24	MNSDs n = 23 Haplo n = 23 (1:1 matched control)	MSDs n = 48 MNSDs n = 56 MUDs n = 18
GVHD prophylaxis	CNI + sMTX/MMF	CyA + sMTX	CyA + sMTX	CyA + sMTX + MMF (MNSDs) PTCy-based (haplo)	CyA + sMTX
Overall survival	MSDs 100.00% MNSDs 100.00%	MSDs 70.9%* MNSDs 54.4%* MMRDs 35.9%*	MSDs 25 months† MNSDs 21 months† MUDs 23 months†	MNSDs 61.5%‡ Haplo 63.7%‡	MSDs 84.44%§ MNSDs 82.32%§ MUDs 75.76%§
Acute GVHD	All grades MSDs 11.00% MNSDs 13.00%	All grades/grade III-IV MSDs 45.30/5.30% MNSDs 54.70/16.00% MMRDs 50.00/14.00%	Grade II-IV MSDs 8.00% MNSDs 21.00% MUDs 8.00%	All grades MNSDs 38.80% Haplo 52.90%	All grades MSDs 10.64% MNSDs 10.91% MUDs 38.89%
Chronic GVHD	MSDs 0.00% MNSDs 0.00%	MSDs 26.10% MNSDs 41.50% MMRDs 52.90%	Not described	Not described	MSDs 2.38% MNSDs 3.85% MUDs 17.65%
Relapse rate	Not described	Not described	Not described	MNSDs 37.50% Haplo 10.05%	Not described

* 3-year overall survival rate; † median survival period; ‡ 2-year overall survival rate; § 5-year overall survival rate. Source: Elaborated by the authors.

In summary, our case strongly underscored the importance of estimating the haplotype frequency of patients' HLA, as the availability of MNSDs would be increased when they had frequent allele patterns. However, to optimize the strategies of transplantation from MNSDs, prospective studies in regions where the availability of this type of donor was high, or retrospective studies using large transplantation datasets, were strongly warranted.

CONFLICTS OF INTEREST

Nothing to declare.

DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

No part of this article was created with assistance from artificial intelligence tools.

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DATA AVAILABILITY STATEMENT

Data will be provided upon request.

AUTHOR CONTRIBUTIONS

Conceptualization: Ebisawa K. **Investigation:** Ebisawa K. **Writing:** Ebisawa K. **Supervision:** Takeuchi T. **Final Approval:** Takeuchi T.

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