Current status of HLA haplo-identical transplantation using post-transplantation cyclophosphamide

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Outcomes of HLA haplo-identical transplantation using post-transplantation cyclophosphamide (PT/Cy-haplo) are similar to those of HLA-matched related/unrelated transplantation. Unlike classical HLA haplo-identical transplantation, PT/Cy-haplo does not require expensive T-cell depletion. Furthermore, accumulating evidences, including meta-analysis data, have indicated that PT/Cy-haplo may have a significant advantage over HLA-matched transplantation, concerning the low incidence of clinically significant, moderate-to-severe chronic graft-versus-host disease. This clinical advantage of PT/Cy-haplo could contribute to economic medical benefits by reducing the cost and improve the quality of life of the patients. The establishment of PT/Cy-haplo could necessitate the recalibration of the donor selection algorithm.

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Introduction

Haploidentical donors are being increasingly used as a usable donor source in the absence of HLA-matched related donors, especially with the prevailing global option of HLA haplo-identical transplantation using post-transplantation cyclophosphamide (PT/Cy-haplo). PT/Cy-haplo is being increasingly used in Japan as well, because of its acceptable safety profile. The use of cord blood for treating acute myeloid leukemia is decreasing in Europe.¹

What is the PT/Cy-haplo system?

In PT/Cy-haplo, activated host-donor allo-reactive T cells proliferate in response to host-donor, dual allogeneic antigen stimulation. These cells can be selectively and efficiently eradicated by high dosage of Cy in a narrow time window, on days 3 or 4 after transplantation, because these T cells are sensitive to Cy. Therefore, tolerance of dual alloreactive

T-cells can be induced by PT/Cy-haplo.²

In contrast, non-reactive T-cells that could be responsible for graft-versus-leukemia (GVL) effects, and protection against post-transplantation infection is spared because these T-cells are not sensitive to Cy. In PT/Cy-haplo, administration of tacrolimus and mycophenolate mofetil (MMF) is initiated after PT/Cy administration to avoid the blockage of Cy-induced tolerance.²

Prospective clinical studies of PT/Cy-haplo

Many prospective studies of PT/Cy-haplo have been reported,³⁻⁹ including a Japanese multi-center trial. These studies have demonstrated the safety and efficacy of PT/Cy-haplo, irrespective of the type of source [bone marrow (BM) or peripheral blood (PB)] (Table 1).

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Table 1. Prospective studies of HLA haplo-identical transplantation using post-transplantation cyclophosphamide

Author	n	Type of graft	GVHD prophylaxis	II–IV aGVHD	cGVHD	Overall Survival
Munchel et al. ³	210	BM	CY50x2, Tac+MMF	27%	13%	60% at 1 year 48% at 2 year 41% at 3 year
Solomon et al. ⁴	20	PBSC	CY50x2, Tac+MMF	30%	35%	69% at 1 year
Solomon et al. ⁵	30	PBSC	CY50x2, Tac+MMF	43%	56%	78% at 2 year
Gaballa S et al. ⁶	60	BM	CY50x2, Tac+MMF	28%	24% (2ys)	70% at 1 year
Brunstain et al. ⁷	50	BM	CY50x2, Tac+MMF	32%	13% (1ys)	62% at 1 year
Sugita et al. ⁸	31	PBSC	CY50x2, Tac+MMF	23%	15% (1ys)	45% at 1 year
Nakamae et al. ⁹	20	PBSC	CY25x2, CY 25 Tac+MMF	60%	10%	64% vs 44% at 1 year

BM, bone marrow; PBSC, peripheral blood stem cell; CY, clophosphamide; Tac, tacrolimus; MMF, mycophenolate mofetil.

Comparison of outcomes after PT/Cy-haplo and HLA-matched related transplantation in a meta-analysis of case-control studies

A recent meta-analysis compared PT/Cy-haplo and HLA-matched related transplants in nine case-control studies that included over 2,000 patients.¹⁰ In terms of acute graft-versus-host disease (GVHD), non-relapse mortality, relapse, progression-free survival (PFS), and overall survival (OS), no differences between PT/Cy-haplo and HLA-matched transplant were evident. In addition, PT/Cy-haplo was significantly related to a lower occurrence of moderate-to-severe chronic GVHD. The meta-analysis findings suggested similar outcomes, except moderate-to-severe chronic GVHD, in case of PT/Cy-haplo and HLA-matched transplants. The findings indicate that PT/Cy-haplo might have an advantage over HLA-matched transplants, because the former is associated with a low incidence of moderate-to-severe chronic GVHD.

Dilemma of classical HLA haplo-identical transplantation

Non-selective T-cell depletion from the graft, through *in vivo* or *ex vivo* depletion, can delay immune reconstitution and increase immunosuppression. T-cell depletion is associated with increased risks of infection and relapse. On the contrary, weak *in vivo* or *ex vivo* depletion of T-cells results in a high incidence of GVHD; optimal T-cell modulation by *in vivo* or *ex vivo* depletion is very difficult. The difficulty in determining the optimal level of T-cell depletion could be a dilemma in classical HLA haplo-identical transplantation.

Theoretically, using PT/Cy can selectively eradicate alloreactive T-cells, which leads to a low incidence of GVHD and

does not disrupt immune reconstitution. In addition, the high discontinuation rate of immune suppressants may contribute to a low transplantation-related mortality, which is synergistic with the low incidence of GVHD.

Cellular mechanisms of T-cell reconstitution following PT/Cy-haplo

Based on the results of a clinical study conducted by an Italian group, the role of naïve-derived T memory stem cells (TSCMs) is considered crucial in T-cell reconstitution following PT/Cy-haplo.¹¹ Proliferating T cells are preferentially depleted by Cy on day 3 or 4 after transplantation. TSCMs, which are likely to be derived from naïve T-cells that were not eradicated by using PT/Cy, is the dominant peripheral T-cell subset one week after transplantation. In the subsequent weeks, naïve-derived TSCMs will produce memory cells by responding to exogenous antigens. Donor naïve T-cells specific for exogenous and self/tumor antigens remain in the host and largely contribute to immune reconstitution after PT/Cy-haplo.

HLA-haploidentical blood or marrow transplantation with high-dose post-transplant cyclophosphamide at Johns Hopkins Hospital

A total of 375 patients received PT/Cy-haplo, using a non-myeloablative transplantation approach, at the Johns Hopkins Hospital (Baltimore, MD, USA) between 2004 and 2012. Recently, the results for 236 patients who underwent this treatment between 2004 and 2009 were reported.¹² The cumulative incidence of acute GVHD was 28% for grades II–IV and 4% for grades III–IV, representing an extremely good control.

Figure 1. Does an excessive dose of PT/Cy partially overshadow graft-versus-leukemia (GVL) effects? Using an excessive dose of cyclophosphamide post transplantation may reduce the effects of GVL to some extent due to the robust elimination of alloreactive T-cells caused by the high dose of cyclophosphamide. The approach may result in the increase of the relapse rate.

The cumulative incidence of non-relapse mortality was as low as 18%. However, the relapse rate was 52%, which is high, and is still a major issue to overcome. Use of bone marrow and/or weak conditioning may have been associated with the high relapse rate.

Refined Disease risk index (DRI)-stratified outcomes in PT/Cy-haplo

The refined DRI is an important indicator of the transplant outcome. A report comparing the outcomes between PT/Cy-haplo and HLA-matched bone marrow transplant from the group at Johns Hopkins showed comparable refined DRI-stratified outcomes.¹³ In patients in the low, intermediate, and high/very-high risk groups, the 3-year event-free survival of PT/Cy-haplo and HLA-matched bone marrow transplantation were 65% vs. 66%, 39% vs. 31%, and 25% vs. 15%, respectively.

Does an excessive dose of PT/Cy partially overshadow graft-versus-leukemia (GVL) effects?

Alloreactive T-cells may be at least partially relevant in GVL effects. We are considering the possibility that the GVL effects may be diminished to some extent by an excessive dose of Cy. Especially in cases of active disease, a strong eradication of alloreactive T-cells using high-doses of Cy may increase the relapse rate (Figure 1).

Grade II acute GVHD improves PFS after PT/Cy-haplo

The high relapse rates noted with PT/Cy use may be associated with low rates of GVHD. The Johns Hopkins Hospital data demonstrated a significant relationship between mild grade II acute GVHD (also termed “good GVHD”) and a lower incidence of relapse and better probability of survival.¹⁴ These results also imply that GVHD and GVL cannot be clearly separated. Thus, we speculate that the suppressive effects of GVHD by PT/Cy use might, to some extent, contribute to the elimination of the GVL effects, as described above.

Comparison of mobilized peripheral blood stem cells and unstimulated bone marrow as a graft source for PT/Cy-haplo

A retrospective study evaluated the difference between the impact of outcomes of using PB and BM for PT/Cy-haplo. There were no significant differences in OS and non-relapse mortality.¹⁵ Incidences of grade II-IV acute and chronic GVHD were higher in case of PB. On the other hand, the risk of relapse was higher after BM transplant in patients with leukemia. Acute and chronic GVHD, which were more frequently observed after the transplantation of PB than of BM, might contribute to graft-versus-tumor effects. However, this analysis was adjusted for acute and chronic GVHD. Thus, the observed lower relapse risk in the PB group could not be sim-

ply explained by the higher incidences of GVHD.

Strategy for PT/Cy-haplo in our institute

We hypothesized that PT/Cy use partially reduces GVL effects. Thus, to achieve substantial disease control, we have made unique modifications. These include intensified conditioning, use of peripheral stem cells as the only stem cell source, and a reduced dose of PT/Cy.⁹ We are currently performing a prospective study using a total Cy dose of 75 mg/kg, with 50 mg/kg on day 3 and 25 mg/kg on day 4 (protocol: OCU16-2).

Incidences of various infections following PT/Cy-haplo

Although the incidences of infections including those due to bacteria and fungi in case of PT/Cy-haplo appeared to be higher than those in case of HLA-matched sibling transplantation, the incidences of infection in case of PT/Cy-haplo were comparable to those in case of HLA-matched and-mismatched unrelated transplantations, and unrelated cord blood transplantation.¹⁶

In terms of viral infections, the incidences of HHV6 reactivation at day 100 were significantly higher, but those of EBV reactivation at day 100 were significantly lower in case of PT/Cy-haplo, than those in patients that received cells from matched or mismatched unrelated donors.¹⁷ The incidence of BK virus-associated cystitis varied from 11% to 75% in case of PT/Cy-haplo.^{4,18-20} Factors affecting the incidence of BK virus-associated cystitis included previous transplants and the occurrence of cytomegalovirus reactivation before cystitis.²⁰ In addition, BK virus-associated cystitis obviously tended to occur at a high frequency in patients receiving high-dose busulfan-containing regimen.

Impact of HLA disparity in haploidentical bone marrow transplantation followed by PT/Cy administration

Whether a different degree of HLA matching could affect outcomes in the PT/Cy-haplo setting is unknown. An Italian group analyzed 318 consecutive patients who received PT/Cy-haplo with BM, and reported that the number of HLA-mismatched antigens did not influence OS and non-relapse mortality.²¹ In addition, uni-vectorial graft-versus-host mis-

matches were not related to the cumulative incidence of acute and chronic GVHD and relapse. Likewise, there was no significant relationship between the degree of HLA mismatch in the HVG direction and graft rejection.

PT/Cy use after bone marrow transplantation is not associated with an increased risk of donor-derived malignancy

Administering high-dose cyclophosphamide immediately after transplantation could theoretically cause the development of malignancy by disturbing the graft at a time of increased hematopoietic stress.²² Importantly, a competing risk analysis recently reported an estimated cumulative incidence of donor-derived malignancy of 1.4%.¹⁷ The rate did not appear to be high when compared to other transplants, suggesting that using PT/Cy after bone marrow transplantation may not drastically increase the risk of donor-derived malignancy; however, further follow-ups will be required for the confirmation of this finding.

Conclusions

PT/Cy-haplo has several advantages, including readily available donors, lack of need for expensive or complicated T-cell depletion procedures, and demonstrated safety, mainly because of the low incidence of GVHD.

Recently, the use of PT/Cy-haplo has been increasing globally. If the safety profiles and feasibility of PT/Cy-haplo are confirmed prospectively, a paradigm shift in alternative donor selection could be necessary.

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Conflict of interest disclosure

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