Post-transplantation Cyclophosphamide: From HLA-Haploidentical to Matched-Related and Matched-Unrelated Donor Blood and Marrow Transplantation

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Following allogeneic blood and marrow transplantation (BMT), graft-versus-host disease (GvHD) continues to represent a significant cause of treatment failure, despite the routine use of conventional, mainly calcineurin inhibitor-based prophylaxis. Recently, post-transplant cyclophosphamide (PTCy) has emerged as a safe and efficacious alternative. First, omitting the need for ex vivo T-cell depletion in the setting of haploidentical transplantation, growing evidence supports PTCy role in GvHD prevention in matched-related and matched-unrelated transplants. Through improved understanding of GvHD pathophysiology and advancements in drug development, PTCy emerges as a unique opportunity to design calcineurin inhibitor-free strategies by integrating agents that target different stages of GvHD development.

Keywords: GvHD prevention, post-transplant cyclophosphamide, matched-related donor, matched unrelated donor, bortezomib, calcineurin inhibitor-free

INTRODUCTION

Despite continued improvement in the outcomes of allogeneic blood and marrow transplant (BMT) over the last decade, the prospects of acute and chronic graft-versus-host disease (aGvHD and cGvHD) continue to drive treatment-related mortality (TRM) and limit the utility and wide applicability of this valuable treatment modality (1). Conventional combinations of calcineurin (CN) or mammalian target of rapamycin (mTOR) inhibitors, coupled with either methotrexate (MTX) or mycophenolate mofetil (MMF), achieve rates of aGvHD and cGvHD of approximately 40–75% and 40–70% following matched-related donor (MRD) and matched-unrelated donor (MUD) transplants (2). In addition to their partial efficacy, these regimens target T-cells broadly and indiscriminately, therefore delaying immune reconstitution and hampering graft-versus-leukemia (GvL) effect. Furthermore, both CN inhibitors (CNI) and mTOR inhibitors (mTORI) have a narrow therapeutic index with multiple drug interactions rendering prescriber experience and patients’ compliance essential for their safety and efficacy (3). Lastly,
as these agents are administered for 6 to 9 months, they typically prevent early post-transplant introduction of interventions and small molecules aimed to decrease the risk of disease relapse.

Post-transplant cyclophosphamide (PTCy), initially developed to overcome human leukocyte antigen (HLA) barriers in the setting of haploidential transplantation (4), has proved promising following MRD and MUD transplants (5–7). Furthermore, PTCy may represent an ideal platform for the development of CN and mTORI-free GvHD prevention strategies.

**MECHANISMS of PTCy In GVHD PREVENTION**

Cyclophosphamide is an alkylating agent that acts through its metabolites, phosphoramidate and acrolein, to induce DNA strand breakage that ultimately leads to replication stress in rapidly dividing cells (8). The efficacy of cyclophosphamide appears to be cell-cycle dependent and is highest in the G1 and S phases (9). In studies evaluating the specific effects of cyclophosphamide on cytotoxic T-cell lines, Strauss et al. observed that increased apoptosis, mediated by increased Fas expression, may differentiate cyclophosphamide from other immunosuppressive agents (4, 10, 11).

The biological underpinnings of PTCy-induced immune tolerance have yet to be fully elucidated. However, there is evidence to support that PTCy eliminates alloreactive T-cell clones of both donor and host origin in the early post-transplantation period with relative preservation of regulatory T-cells (12, 13). This is supported by early evidence from murine skin allograft experiments where allografted mice were treated with cyclophosphamide shortly after engraftment. In these test animals, donor-derived alloreactive T-cell populations were eliminated via extra-thymic mechanism, presumably related to cyclophosphamide administration (14, 15). Simultaneously, regulatory T-cells were selectively spared, possibly due to their expression of a specific aldehyde dehydrogenase that confers resistance to cyclophosphamide (16, 17). Life-long immune tolerance was subsequently maintained by central, intra-thymic clonal deletion of the anti-host T-cells derived from donor hematopoietic stem cells.

The previously demonstrated pivotal role of regulatory T-cells in PTCy-induced immune tolerance was recently corroborated by a series of experiments performed by Waschmuth et al. Mice treated with PTCy at 25 mg/kg on day +3 and +4 following haploidential transplantation showed significantly less severe GvHD than mice treated with 5 or 100 mg/kg a day. In these experiments, immune tolerance developed despite the persistence of alloreactive T-cells following optimally dosed PTCy and in the absence of thymus. Rather than eliminating alloreactive T-cells, PTCy induced functional impairment of these cells, supported by robust suppressive mechanisms that included rapid and preferential recovery of regulatory T-cells (18, 19). Further validation of these mechanisms will improve our understanding of PTCy-induced immune tolerance and identify the optimal dosing of cyclophosphamide.

**PTCy IN HAPLOIDENTIAL TRANSPLANT**

An early study established that PTCy can overcome HLA barriers and omit the need for *ex vivo* T-cell depletion following a non-myeloablative preparative regimen and haploidential bone marrow transplant (20, 21). In this trial, the investigators compared one dose of PTCy administered on day +3 and two doses of PTCy on day +3 and +4, demonstrating a decreased incidence of cGvHD in the group receiving two doses (25% versus 5%, *p* = 0.05%) with no differences in aGvHD, event-free survival (EFS) or overall survival (OS). The incidence of grades II-IV and III-IV aGvHD for the entire cohort was 34 and 6%, respectively (21). This data was confirmed in a larger study conducted by Kasamon et al. and Munchel et al. In a cohort of 210 patients, the incidence of grades II-IV acute and cGvHD were 27 and 13%, respectively (22, 23). The rates of disease relapse, EFS, and OS were 55, 35, and 27%, respectively.

Following the initial studies, which were focused on bone marrow as the graft source, the safety and efficacy of PTCy-based GvHD prevention were validated following both myeloablative and non-myeloablative conditioning regimens by several investigators. In a study by Solomon et al. using busulfan-based myeloablative conditioning, the incidence of grade II-IV and III-IV aGvHD and cGvHD were 30, 10, and 35% (24). Similar results were reported by Bhamidipati et al. following a non-myeloablative preparative regimen (25). More recently, Wang et al. showed that the addition of low dose PTCy (14.5 mg/kg on day +3 and +4), to the so-called Beijing protocol, reduced the incidence of grade II-IV aGvHD and improved GvHD- and relapse-free survival (GRFS) (26).

Based on these studies and others, haploidential transplantation has become, with the advent of PTCy, one of the most commonly used alternative donor strategies. Multiple retrospective comparisons have demonstrated similar overall survival of haploidential transplantation to that of HLA-matched donor and cord blood transplants (27).

**PTCy AS MONOTHERAPY IN MRD AND MUD TRANSPLANT**

Since establishing its role in the haploidential setting, several investigators examined the applicability of PTCy to GvHD prevention in MRD and MUD transplants. Luznik et al. reported the incidence of acute and cGvHD following myeloablative conditioning in 117 recipients of MRD (*n* = 78) and MUD (*n* = 39) bone marrow grafts. In this study, GvHD prophylaxis consisted of a single agent PTCy. Grades II-IV and III-IV acute GvHD rates were 43 and 10% for the entire cohort. The long-term incidence of cGvHD was particularly low at 10%. EFS sand OS were 55 and 39% (5). Interestingly, 43% of patients did not require any other form of immunosuppressive therapy (28). These favorable results were corroborated by a similar multi-institutional trial by Kankary et al. with a low incidence of cGvHD at 14% (6).
Unfortunately, when Alousi et al. examined PTCy as the only GvHD prophylaxis following reduced-intensity preparative regimen and peripheral blood grafts, the results were strikingly different (29). In this study, 38 patients received bone marrow and 11 patients received peripheral blood grafts. Twenty-two patients received rabbit anti-thymocyte globulin (rATG) before the study was amended to omit rATG. The rates of grade II-IV and grade III-IV aGVHD were 58% and 22%, whereas the rate of cGVHD was 18%. When the authors compared the results to a matched, historical cohort of patients receiving TAC and MTX for GvHD prophylaxis, significantly higher rates of all grades of aGvHD [46% vs. 19%, hazard ratio (HR) = 2.8, p = 0.02] as well as inferior TRM (HR = 3.3, p = 0.035) and OS (HR = 1.9, p = 0.02) were observed in the PTCy cohort. There were no differences in cGVHD between the prospectively treated patients and the historical control (29). Similarly, unsatisfactory results were reported in a smaller phase II study by Holtick et al. (30). The authors examined the safety and efficacy of PTCy as monotherapy for GvHD prevention following reduced-intensity conditioning and MRD and MUD peripheral blood grafts. The rate of TRM was unacceptably high at 36%, principally attributable to an increased rate of severe intestinal aGVHD. A study by Bradstock et al. was terminated early when four out of the first five patients developed life-threatening aGVHD, two of whom died (31).

Cumulatively, the current evidence suggests that, while single-agent PTCy may represent a viable prophylactic option in patients receiving myeloablative conditioning and bone marrow graft, it is inadequate in the setting of reduced-intensity conditioning and peripheral blood transplantation.

**PTCy AND CNI OR mTOR INHIBITORS IN MRD AND MUD TRANSPLANT**

Given the shortcomings of PTCy as monotherapy for GvHD prophylaxis following MRD and MUD peripheral blood transplants, several groups reverted to combining PTCy with a CNI or mTORI with or without MMF, aiming to reduce the relatively high incidence of cGVHD characteristic of CNI and mTOR inhibitors-based combinations. To this end, Mierlcarek et al. combined PTCy with cyclosporine A (CSA) in patients receiving myeloablative conditioning. The rates of grades II-IV and III-IV aGVHD were favorable at 77 and 0% and again with a low incidence of cGVHD at 16%. The rates of TRM and disease relapse were 14 and 17% (32). Moiseev et al. compared the outcomes of patients receiving a combination PTCy, TAC and MMF to the outcomes of consecutive historical control patients receiving TAC, MMF and rATG following myeloablative conditioning and MUD or 1–2 HLA loci mismatched-unrelated donor peripheral blood grafts. The rates of grades II-IV and III-IV aGVHD were 19% vs. 45% (p = 0.003) and 4% vs. 27%, (p < 0.001), respectively. The incidence of cGVHD was 16% vs. 65% (p < 0.001). EFS and OS were also improved in the PTCy group (HR = 0.49, 95% CI 0.31–0.78, p = 0.006, and 0.43, 95% CI 0.26–0.7, p = 0.007) (33). Carnevale-Schianca et al. employed the same GvHD prevention regimen in 35 patients receiving RIC.

### TABLE 1 | Selected registered studies of PTCy-based GvHD prevention in MRD and MUD transplantation.

| Study identification | Study type | Intervention | Responsible party |
|----------------------|------------|--------------|-------------------|
| NCT04202835 Phase III, Randomized | rATG versus rATG and PTCy | Sarah Kleiboer |
| NCT04232885 Phase II | PTCy, tacrolimus, and MMF in patients with primary bone marrow failure or immunodeficiency syndromes | Orly Klein |
| NCT03571958 Phase II | PTCy and rATG | Arnon Nagler |
| NCT02811220 Phase II | PTCy and sirolimus in patients with chronic granulomatous disease | Elizabeth Kang |
| NCT02814127 Phase II | PTCy, tacrolimus and MMF | Uday Popat |
| NCT03193297 Phase II | PTCy, sirolimus and MMF | Christine Ho |
| NCT0818334 Phase III, Randomized | rATG, CNI, and MMF versus PTCy, CNI and MMF | Andrea Fesioa Ribeiro |
| NCT03945691 Phase II | PTCy, bortezomib and rATG | A Samer Al-Homsri |
| NCT03602898 Phase II | CNI and MTX versus CNI, MTX, and rATG or PTCy and CNI | Masumi Ueda |
| NCT03959241 Phase III, Randomized | Tacrolimus and MTX versus PTCy, tacrolimus and MMF (GvHD prevention and stool microbiome) | Mary Horowitz |
| NCT03585851 Phase I | PTCy (pharmacogenetics predictors of efficacy) | Chojecki, Aleksander |
| NCT03284900 Phase II | Cyclosporine, sirolimus, and MMF versus PTCy, cyclosporine, and sirolimus | Masumi Ueda |
| NCT03263767 Phase II | PTCy | Patrice Celivallier |
| NCT04160390 Phase II | PTCy (biomarkers predictors of efficacy) | Jeanine McCune |
| NCT03680092 Phase II | Tacrolimus and MTX versus PTCy and abatacept | Divya Koura |
| NCT02558931 Phase II | PTCy, tacrolimus (short course) and MMF | Amy E. Dezern |
| NCT02787679 Phase II | Cyclosporine, MMF and rATG versus PTCy, cyclosporine, and MMF | Mohammad Mothy |
| NCT02938095 Phase II | PTCy, tacrolimus, and MMF in patients with severe aplastic anemia | Amy E. Dezern |

*rATG, rabbit anti-thymocyte globulin; MMF, mycophenolate mofetil; MTX, methotrexate.*
and MRD, MUD, or 1 HLA locus mismatched-unrelated donor peripheral blood transplants. The patients achieved grades II-IV aGvHD and cGvHD rates of 17 and 7% with no grade IV aGvHD. The 2-year TRM rate was 3% with EFS and OS rates of 54% and 77% (34).

Two studies examined the combination of PTCy and sirolimus. Solomon et al. conducted a phase II study that included 26 patients treated with RIC following MUD and peripheral blood transplants. Sirolimus was stopped without taper between day +90 and 100. The rates of grade III-IV acute and cGvHD were higher than the aforementioned rates with PTCy and CNI combinations at 16 and 31% (35). Greco et al. elaborated on the use of PTCy in combination with sirolimus in 28 patients receiving a myeloablative preparative regimen and MRD or MUD peripheral blood allografts. MMF was added to the regimen in patients receiving MUD transplants. The incidence of grades II-IV acute and cGvHD seemed better at 23 and 13% (36).

The most substantial evidence favoring a PTCy-based GvHD prevention strategy in the setting of MRD or MUD donor transplants stems from a recent Blood and Marrow Transplant Clinical Trial Net randomized phase II trial (37). In this trial patients received RIC and were randomized to one of three GvHD prevention regimens: TAC, MTX, and bortezomib, TAC, MTX and maraviroc or PTCy, TAC, and MMF. Patients with MRD, MUD, or 1 HLA locus mismatched-unrelated donors were included. Each of the trial’s three groups was then compared to a contemporaneous prospective control group receiving TAC and MTX from non-participating institutions. Comorbidities were more frequent in the control group. The distribution of the conditioning regimens was also different. Among the three groups, only the group treated with PTCy-based prophylaxis had better outcomes in comparison to the control cohort. The rates of grades II-IV and III-IV aGvHD for the PTCy group were 27% (90% CI 20%–35%) and 2% (90% CI 0–5%). The corresponding rates in the control group were 30% (90% CI 25%–36%) and

![Mechanism of action of agents that may conceptually be added to PTCy to develop CN and mTORI-free combinations for GvHD prevention. DAMPS, damage-associated molecular patterns; PAMPS, pathogen-associated molecular patterns; BOR, bortezomib; ABA, abatacept; MHC II, major histocompatibility complex class II; UST, ustekinumab; TGF-β, transforming growth factor-β; HSC, hematopoietic stem cells; VEDO, vedolizumab; NATA, natalizumab.](image-url)
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When compared to a registry control group the 1-year GRFS was 45.3% (95% CI 20%–36%) and 28% (95% CI 33%–43%), respectively. The 1-year GRFS rates were also superior in the PTCy group (HR = 0.72, 95% CI 0.54–0.94, p = 0.044). However, there was no difference in TRM, DFS, and OS. These results were corroborated by a prospective randomized trial comparing CSA and MMF to PTCy and CSA following MRD and MUD peripheral blood transplants. The group receiving PTCy-based GvHD prophylaxis had lower rates of acute and cGvHD and improved GRFS (38).

In summary, pending the results of an ongoing phase III randomized trial (CTN03959241), comparing PTCy in combination with TAC and MMF to TAC and MTX, PTCy in combination with a CNI for GvHD prophylaxis may potentially emerge as a new standard of care for the prevention of GvHD in the setting of MRD and MUD transplantation.

**PTCy AS A PLATFORM FOR CN AND mTOR INHIBITOR-FREE GvHD PREVENTION IN MRD AND MUD TRANSPLANT**

Given the previously mentioned pitfalls of CN and mTOR inhibitor-containing GvHD prevention regimens, our work over the last several years focused on exploiting PTCy in order develop CN and mTOR inhibitor-free GvHD preventive combinations.

Proteasome inhibitors have multiple immune modulatory effects that span different stages of GvHD development including dendritic and T-cell differentiation, proliferation and function. Proteasome inhibitors also foster the expansion of regulatory T-cells (39, 40). Despite the fact that the results of a recent phase II trial examining the combination of bortezomib with CN and mTORI compared to a standard TAC and MTX combination were disappointing (41), we hypothesized based on pre-clinical data that proteasome inhibitors remain appealing agents when paired with PTCy. In a murine model, the combination of PTCy and ixazomib resulted in superior survival of animals subjected to lethal GvHD in comparison to either drug alone. Furthermore, PTCy prevented the surge in cytokine suppression including IL-6, IL-1β, and tumor necrosis factor-α (42). In a clinical trial, bortezomib was added to PTCy in MRD and MUD transplantation following RIC and peripheral blood grafts. Patients receiving MUD transplantation also received r-ATG. Two doses of bortezomib were given 6 h after graft infusion and 72 h thereafter. All GvHD prophylaxis was completed on day +4. The rates of aGvHD grades II to IV and III to IV were 35.9% (95% CI 18.6–53.6%) and 11.7% (95% CI 2.8%–27.5%). The rate of cGvHD was 27% (95% CI 11.4%–45.3%). The 2-year GRFS was 37.7% (95% CI 20.1%–55.3%) (43). When compared to a registry control group the 1-year GRFS was 39% (95% CI 24%–54%) in the study group and 32% (95% CI 27%–38%) in the control group (HR = 0.81, 90% CI 0.52–1.27, p = 0.44) (unpublished data). These promising results are being confirmed in a larger trial.

**Table 1** provides a summary of selected registered studies that use PTCy-based GvHD prevention in MRD and MUD transplantation.

**FUTURE DIRECTIONS**

Improving upon our understanding of GvHD pathophysiology and our advancement in drug development offer additional opportunities to rationally design CN and mTORI-free PTCy-based GvHD prevention combinations following MRD and MUD transplantation. Toward this end, T-cell co-stimulation blockade, integrin antagonists and IL-23 inhibitors seem attractive as these agents target different phases of GvHD development (Figure 1). Abatacept, a soluble fusion compound of cytotoxic T-cell associated antigen-4 (CTLA-4) and immunoglobulin G1 (IgG1) that binds to CD80 and prevents dendritic cells from delivering a second stimulation signal for T-cell activation, reduced the incidence of aGvHD when added to a standard combination of CNI and MTX in patients receiving matched or one HLA locus mismatched-unrelated donor transplantation (44). Anti-integrin therapy, on the other hand, prevents T-cell trafficking into the guts. Vedolizumab, which acts on a gut-trophic α4β7 integrin and natalizumab, which acts on α4-integrin are being examined in GvHD prevention and treatment (45, 46). Lastly, IL-23 subunit p40 antagonist, ustekinumab, polarizes T-cell differentiation thus preventing the development of T-helper 1 (Th1) and T-helper 17 (Th17) and favoring the expansion of regulatory T-cells is also being studied in GvHD prevention (47). Other IL-23 p19 subunit inhibitors including guselkumab, tildrakizumab and risankizumab may also be of interest. Carefully designed clinical trials are warranted to examine the potential role of these agents in the prevention of GvHD.

**CONCLUSION**

Since establishing its role in HLA-haploidentical transplantation, PTCy has emerged as an effective platform in GvHD prevention strategies in MRD and MUD transplantation. Pending ongoing randomized study, PTCy in combination with TAC and MMF may represent a new standard of care based on its ease of administration and efficacy. Furthermore, PTCy offers a unique opportunity for the development of CN and mTORI-free GvHD preventive combinations, allowing an early introduction of immune manipulations and small molecules aimed to prevent disease relapse following allogeneic BMT.

**AUTHOR CONTRIBUTIONS**

All authors contributed to the writing of the manuscript.
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**Conflict of Interest:** AA-H received research support from Millennium Pharmaceuticals.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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