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# Have We Achieved a Goldilocks Grade of Graft-Versus-Host Disease?

Sumithira Vasu*, Samantha Jaglowski

*Division of Hematology, The Ohio State University, Columbus, Ohio*

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Posttransplantation cyclophosphamide (PTCy) has enabled near-universal donor access and expanded the pool of patients eligible for a haploidentical allogeneic transplant. Although often used in combination with a calcineurin inhibitor (CNI), it can be used as sole graft-versus-host disease (GVHD) prophylaxis in HLA-identical transplantation following myeloablative conditioning. Previous approaches using CNI-free approaches have included ex vivo T cell depletion using immunomagnetic selection of $CD34^+$ cells and in vivo T cell depletion using antithymocyte globulin [1,2].

The article by McCurdy et al. [3] evaluates the incidence of GVHD when PTCy is used as a sole GVHD prophylaxis in the setting of a myeloablative bone marrow transplant (BMT). The authors report a retrospective review of 298 adult recipients, 187 of whom received a matched sibling donor (MSD) graft and 111 from a matched unrelated donor (MUD) from a single institution. All patients received a marrow graft with a goal dose of $4 \times 10^8$/kg following conditioning with busulfan combined with either fludarabine or cyclophosphamide and followed by PTCy on days +3 and 4. The authors describe in granular detail the impact of no GVHD versus grade II acute GVHD (aGVHD) versus grade III to IV aGVHD and chronic GVHD (cGVHD) on outcomes such as overall survival (OS), progression-free survival (PFS), nonrelapse mortality, and relapse. It is important to note that 58% of patients had active disease or measurable residual disease at the time of transplant. Day 100 incidence of grade II aGVHD was 35% in MSD and 57% in MUD recipients. As expected, 58% of patients with grade II aGVHD had skin-only involvement, 14% of whom progressed to grade III to IV GVHD, whereas 42% of patients had gut or liver involvement without skin involvement, 31% of whom progressed to grade III to IV GVHD. The median onset to GVHD was 33 days in MUD versus 38 days in MSD BMT. In a landmark analysis at 100 days for the entire cohort, 4-year relapse incidence was 33% in those with grade II aGVHD versus 49% in those without GVHD. Four-year OS was 57% and PFS was 40% in those without GVHD versus 68% OS and 54% PFS in those with grade II GVHD. A definite decrease in relapse incidence was observed in those who had grade II GVHD and cGVHD with a resultant increase in OS.

Efforts to dissociate milder grades of aGVHD from cGVHD, particularly the use of regimens that promote a milder form of GVHD along with a reduction in relapse, have been ongoing for several decades (Table 1). The article by McCurdy et al. [3] attempts to look at the severity of GVHD and correlate it with outcomes that truly matter, such as survival, relapse incidence, and need for systemic immunosuppression, and shows that the cohort with grade II aGVHD had the best OS and PFS. Also of interest is the proportion of patients who are not undergoing immunosuppression at 1 year, which establishes the severity and duration of GVHD while reflecting long-term morbidity from the immunosuppressive burden of patients. The role of systemic immunosuppression for grade II skin-only GVHD is brought into question. Does treatment with steroids for grade II aGVHD abrogate graft-versus-leukemia (GVL) and should steroids be reserved for patients with grade III to IV aGVHD or those more likely to progress? The recently completed BMT clinical trials network (CTN) study 1501 (NCT02806947), using a biomarker-based strategy for lower-risk GVHD, randomized patients between sirolimus and prednisone as first-line treatment. Early data show comparable response rates between the 2 groups. As the data mature from this study, we may have additional information on the role of steroids as first-line treatment for lower-risk GVHD.

McCurdy et al. [3] show that PTCy alone is an effective GVHD prophylaxis agent in MSD and MUD following myeloablative conditioning, lowering the incidence of severe grade III to IV GVHD and cGVHD, along with relapse in those with grade II GVHD. Recent studies have shown that in addition to eliminating alloreactive T cells, PTCy also helps restore the balance of T regs in the reconstituting immune system, hence promoting tolerance, and lowers the incidence of cGVHD. Mechanistic studies are required to parse out GVL effects with PTCy. This report showing that higher-grade GVHD rates can be lowered while preserving mild forms of GVHD without negatively affecting relapse is tantalizing. Comparisons between the different CNI-free approaches using retrospective studies fall short due to differences in reporting of outcomes, heterogeneity of hematologic malignancies, and disease status at the time of transplant.

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* Correspondence and reprint requests: Sumithira Vasu, The Ohio State University, B 316 Starling-Loving Hall, Columbus, OH 43210.
*E-mail address:* Sumithira.vasu@osumc.edu (S. Vasu).

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**Table 1**
Outcomes Using Current Immunosuppressive Approaches in Myeloablative HCT for AML

| Characteristic | ATG [2], % | TCD [2], % | PTCy [3], % | |
|---|---|---|---|---|
| | | | MSD | MUD |
| 100 days | | | | |
| Grade II-IV GVHD | 21 | 11.3 | | |
| Grade II GVHD | | | 35 | 57 |
| Grade III-IV GVHD | | | 11 | 14 |
| 1 year | | | | |
| Chronic GVHD | 27.6 | 2.5 | 9 | 16 |
| 2 years | | | | |
| Relapse | 30 | 21.6 | | |
| 4 years | | | | |
| Relapse (−GVHD) | | | 49 | |
| Relapse (+GVHD) | | | 33 | |

ATG indicates antithymocyte globulin; TCD, T cell depletion.

Hence, BMT CTN 1301 (NCT 02345850), which randomized patients with acute myelogenous leukemia and myelodysplastic syndrome (MDS) in complete remission receiving myeloablative conditioning to 3 different arms, comparing immunomagnetic T cell depletion versus sole PTCY versus a CNI/methotrexate arm, will be instrumental in evaluating the outcomes of these approaches in a multicenter setting. The primary endpoint of this study is cGVHD/relapse-free survival, and the secondary endpoints of this study are grade II to IV aGVHD. We eagerly await results of this 345-patient study that recently completed accrual. In the meantime, the article by McCurdy et al. [3] evaluating PTCy as a sole immunosuppressive strategy raises optimism that grade II aGVHD may be differentiated from grade III to IV aGVHD as a clinical trial endpoint and that systemic treatment of grade II skin-only aGVHD may not be necessary. The next challenge will be to build on this platform, devising ways to decrease opportunistic infections and relapse.

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