blood advances

PTCy unchained in matched siblings: the D is silent in GVHD

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In this issue of *Blood Advances*, the study from Desai et al[1] shows signals of potential feasibility when posttransplant cyclophosphamide (PTCy) is used as graft-versus-host disease (GVHD) prophylaxis compared with traditional regimens in the matched sibling transplant setting.

Hematopoietic stem cell transplantation (HSCT) has evolved appreciably over several decades, yet GVHD remains a formidable challenge, affecting 30% to 60% of transplant recipients and being still the leading cause of nonrelapse mortality after HSCT.[2] PTCy, which has shown initial success in the haploidentical and mismatched unrelated transplant settings, has gained increasing attention in the matched sibling donor and matched unrelated donor transplant settings. Although effective in reducing GVHD, PTCy as a standalone agent has shown limitations, leading to the exploration of combination regimens, such as with calcineurin inhibitors (CNI), methotrexate (MTX) or mycophenolate mofetil (MMF), or antithymocyte globulin (ATG). When compared with non–PTCy-based conventional regimens, PTCy-based regimens (with or without serotherapy) have shown remarkable efficacy to minimize the risk of GVHD without increasing the risk of leukemic relapse after matched unrelated donor or, mismatched/haploidentical donor transplants. However, such efficacy has not been explored in large-scale studies of matched sibling transplants. There is also a hypothetical risk of compromising the graft-versus-leukemia effect in the matched sibling transplant setting when using a PTCy-based regimen.

In the study by Desai et al, they evaluated 413 patients undergoing matched sibling transplants (graft source: peripheral blood) from 2010 to 2023, and categorized the patients into 4 groups based on their GVHD prophylaxis regimen: group 1 (CNI with MTX or MMF), group 2 (CNI, MTX/MMF, and ATG), group 3 (PTCy, ATG, and CNI), and group 4 (PTCy, CNI, and MMF). PTCy-based regimens demonstrated superior outcomes in terms of reducing both acute and chronic GVHD without increasing relapse rates, thereby showcasing their effectiveness. For example, the cumulative incidence of severe acute GVHD was significantly lower in patients receiving PTCy-based regimens, particularly when combined with ATG (group 3) or MMF (group 4). Similarly, moderate-to-severe chronic GVHD incidence was substantially reduced in these groups, highlighting the role of PTCy in mitigating GVHD severity.

Patients receiving PTCy also experienced improved GVHD-free/relapse-free survival (GRFS) at 1 and 2 years, indicating a better overall balance between disease control and quality of life. Importantly, although PTCy was linked to delayed neutrophil and platelet engraftment, this did not translate into increased graft failure, further demonstrating the safety profile of this approach.

Although the addition of ATG to PTCy-based regimens further reduced the incidence of chronic GVHD, it was associated with higher rates of viral reactivations (eg, cytomegalovirus and Epstein-Barr virus) and related complications, highlighting the trade-off between infection risk and GVHD control. This finding should however be taken with a grain of salt because many patients were treated before the letermovir era.[3] Despite that, infection-related nonrelapse mortality was not significantly increased in the group treated with PTCy and ATG compared with the other groups.

Infections, particularly bloodstream infections, were however more frequent in PTCy-treated patients, primarily within the first 60 days after transplant. This underscores the need to: (1) better understand the timing of immune reconstitution after PTCy (plus ATG; which was not analyzed in this study),[4] (2) ensure vigilant infection monitoring, and (3) implement robust prevention strategies when using PTCy-based regimens.

This study provides further evidence to underscore the promise of PTCy beyond the haploidentical setting.[5] Another important factor in this setting is the effect of the GVHD prophylaxis regimen on freedom from posttransplant immunosuppression, which can affect the treatment burden and quality of life. Desai et al report that the median time to discontinue immunosuppression was relatively short (ie, 96 days in patients receiving PTCy). Unfortunately, this study did not report on the actual frequency of patients who were consistently off all immunosuppression. A previous study however reported that PTCy can effectively reduce the immunosuppressive burden compared with CNI-based GVHD prophylaxis, with or without ATG.[6]

Another point to consider when interpreting the results of this study, is the use of ATG and how the efficacy of ATG can vary by formulation. For example, thymoglobulin has previously shown limited benefit, with only ~40% freedom from immunosuppression at 1 year, which is lower than for anti–T-lymphocyte globulin (ATLG).[7,8] For matched sibling donor transplants, ATLG achieved 91% cyclosporine discontinuation by 1 year,[9] similar to PTCy-treated patients, half of whom required no additional immunosuppression after day +4. Taken together, findings from Desai et al position PTCy as a strong alternative to AT(L)G, reducing immunosuppressive burden and GVHD risk. These findings also justify prospective head-to-head comparisons, especially in the matched sibling setting.

Finally, in this study by Desai et al, PTCy (group 4) showed increased survival that was driven by improved nonrelapse mortality, although effects on GVHD were stronger for the combination of PTCy and ATG. This raises the possibility that improved survival may not stem directly from PTCy but rather from unmeasured or confounding factors, such as patient selection or supportive care variations, as highlighted by a previous study demonstrating that the use of PTCy is associated with an increased risk of non-cytomegalovirus herpesvirus infections and thus with increased risk of nonrelapse mortality.[10]

In conclusion, PTCy-based (in addition to ATG) GVHD prophylaxis may represent an attractive option in the matched sibling transplant setting, offering GVHD control and improved GRFS compared with traditional regimens. Although challenges such as infection risks and delayed engraftment persist, Desai et al provide a strong rationale for PTCy as a valuable standard for GVHD prophylaxis across donor platforms. Future studies should also investigate whether such PTCy-based GVHD prevention regimens afford the same results in pediatric patients.

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