

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

1. de Stoppelaar SF, van 't Veer C, Claushuis TAM, Albersen BJA, Roelofs JJTH, van der Poll T. Thrombocytopenia impairs host defense in gram-negative pneumonia-derived sepsis in mice. *Blood*. 2014;124(25):3781-3790.
2. Grewal PK, Uchiyama S, Ditto D, et al. The Ashwell receptor mitigates the lethal coagulopathy of sepsis. *Nat Med*. 2008;14(6):648-655.
3. Semple JW, Italiano JE Jr, Freedman J. Platelets and the immune continuum. *Nat Rev Immunol*. 2011;11(4):264-274.
4. Xiang B, Zhang G, Guo L, et al. Platelets protect from septic shock by inhibiting macrophage-dependent inflammation via the cyclooxygenase 1 signalling pathway. *Nat Commun*. 2013;4:2657-2668.
5. Yin H, Stojanovic-Terpo A, Xu W, et al. Role for platelet glycoprotein Ib-IX and effects of its inhibition in endotoxemia-induced thrombosis, thrombocytopenia, and mortality. *Arterioscler Thromb Vasc Biol* 2013;33(11):2529-2537.
6. Corken A, Russell S, Dent J, Post SR, Ware J. Platelet glycoprotein Ib-IX as a regulator of systemic inflammation. *Arterioscler Thromb Vasc Biol*. 2014;34(5):996-1001.
7. Seok J, Warren HS, Cuenca AG, et al; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci USA*. 2013;110(9):3507-3512.
8. Takao K, Miyakawa T. Genomic responses in mouse models greatly mimic human inflammatory diseases [published online ahead of print August 4, 2014]. *Proc Natl Acad Sci USA*.

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● ● ● TRANSPLANTATION

Comment on Kanakry et al, page 3817

GVHD prophylaxis made safe, easy, and inexpensive

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In this issue of *Blood*, Kanakry and coworkers report on the use of posttransplant cyclophosphamide (Cy) as sole immunoprophylaxis against graft-versus-host disease (GVHD) in HLA-matched related or unrelated allogeneic hematopoietic stem cell transplant (HSCT).¹

This pilot study included 209 consecutive adult patients with acute myeloid leukemia (n = 138), acute lymphoblastic leukemia (n = 43), or myelodysplastic syndrome (n = 28). All patients received T-cell-replete allografts. The cumulative incidence of acute GVHD of grades II-IV at 100 days was 45%; that of acute GVHD of grades III-IV was 11%. In line with experience using posttransplant Cy in haploidentical HSCT, the probability of chronic GVHD was strikingly low (13%). Three-year probability of relapse was 36%. Thirty percent of the patients were not in morphologically complete remission at the time of transplant. At 3 years, disease-free survival was 46% and overall survival was 58%. Transplant-related mortality (TRM) at 3 years was 15% (95% confidence interval: 10-20%) for the entire cohort.

Although the probability of severe acute GVHD was comparable to that using a calcineurin inhibitor combined with a short arm of methotrexate, TRM was low, which may

suggest a low risk of death from infections and toxicity—demonstrating the safety of this protocol.

Advantages of using posttransplant Cy are that it selectively depletes proliferating alloreactive T cells while preserving resting memory T cells, which are essential for immunological recovery after HSCT. This approach is certainly much simpler and less expensive than alternative approaches to improve immune reconstitution after HSCT, such as T-cell depletion and add-back of suicide gene—manipulated T cells, in vitro depletion of alloreactive donor T cells, or the development of cytotoxic donor T cells against cytomegalovirus, adenovirus, Epstein-Barr virus, and fungi, which may cause severe infections after HSCT.²

The team from the Johns Hopkins University pioneered the use of posttransplant Cy to control posttransplant alloreactivity using T-cell-replete grafts and HLA-haploidentical donor transplantation.³ Posttransplant Cy was based on a mouse study in which Luznik and coworkers demonstrated

that posttransplant Cy administered on day +3 allowed stable engraftment across major histocompatibility complex barriers using a nonmyeloablative regimen.⁴ This concept has revolutionized haploidentical transplants, with an increasing number of such transplants being performed worldwide.⁵ The concept of posttransplant Cy in haplo-HSCT has challenged double cord blood transplants⁶ and unrelated donor transplants with similar survivals (Mary Eapen et al, Center for International Blood and Marrow Transplantation Research, unpublished data).

Now the concept of posttransplant Cy has been extended to HLA-matched HSCT.

The low TRM rates with posttransplant Cy may be due to the low rate of posttransplant infections, and there have been no posttransplant lymphoproliferative disorders reported so far with this immunosuppression.^{1,3,5} Using myeloablative conditioning and high-dose busulfan especially, there may be an increased risk of hemorrhagic cystitis using Cy, as found in a prospective, randomized study.⁷ The low risk of chronic GVHD is certainly welcome because it reduces suffering and improves the patients' quality of life. However, chronic GVHD has a strong graft-versus-leukemia effect and reduces the probability of leukemic relapse after HSCT.⁸ It is possible that the low risk of chronic GVHD using posttransplant Cy may be associated with an increased risk of leukemic relapse. The depletion of alloreactive T cells may also deplete leukemia-reactive T cells. Future randomized studies will determine whether this is the case.

Since the Seattle team introduced cyclosporine and a short arm of methotrexate as GVHD prophylaxis, this has been the gold standard for immunosuppressive therapy after HSCT worldwide.⁹ After several decades of immunosuppressive dominance using a calcineurin inhibitor and a short arm of methotrexate post-HSCT, this prophylaxis was challenged by Cutler and coworkers, who introduced a combination of tacrolimus and sirolimus as an alternative.¹⁰ In a randomized study comparing tacrolimus/sirolimus with tacrolimus/methotrexate as GVHD prophylaxis, it was found that the probability of acute and chronic GVHD, relapse, relapse-free survival, and overall survival was similar between the 2 groups. However, there was more rapid engraftment and less oropharyngeal mucositis in the patients treated with sirolimus

instead of methotrexate. In the study by Kanakry and coworkers, using posttransplant Cy as single agent, disease-free survival and survival were similar to those in studies using other immunosuppressive protocols including calcineurin inhibitors.¹ Other factors such as quality of life with less chronic GVHD, better immune function, and lower costs may be of importance when comparing single-agent Cy with other immunosuppression protocols. It is certainly much less expensive to give 2 doses of Cy, 50 mg/kg per day IV, than months of expensive treatment with calcineurin inhibitors. For patients and institutions that cannot afford calcineurin inhibitors, Cy after HSCT is a less expensive alternative. In patients with little education and where drug compliance would be expected to be poor, post-HSCT Cy is a valid alternative to T-cell depletion.

To conclude, single-agent posttransplant Cy appears to be safe, with few infections and low TRM, easy, and inexpensive. Planned prospective randomized studies at our institution—and probably at many other

institutions worldwide—will evaluate the extent to which this is true.

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REFERENCES

1. Kanakry CG, Tsai H-L, Bolaños-Meade J, et al. Single-agent GVHD prophylaxis with posttransplantation cyclophosphamide after myeloablative, HLA-matched BMT for AML, ALL, and MDS. *Blood*. 2014;124(25):3817-3827.
2. Ringdén O, Karlsson H, Omazic B. Immune reconstitution after HLA mismatched haemopoietic stem-cell transplantation. *Lancet Oncol*. 2009;10(5):440-442.
3. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008;14(6):641-650.
4. Luznik L, Jalla S, Engstrom LW, Iannone R, Fuchs EJ. Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide. *Blood*. 2001;98(12):3456-3464.
5. Bashay A, Zhang X, Sizemore CA, et al. T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. *J Clin Oncol*. 2013;31(10):1310-1316.
6. Brunstein CG, Fuchs EJ, Carter SL, et al; Blood and Marrow Transplant Clinical Trials Network. Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. *Blood*. 2011;118(2):282-288.
7. Ringdén O, Ruutu T, Remberger M, et al. A randomized trial comparing busulfan with total body irradiation as conditioning in allogeneic marrow transplant recipients with leukemia: a report from the Nordic Bone Marrow Transplantation Group. *Blood*. 1994;83(9):2723-2730.
8. Horowitz MM, Gale RP, Sondel PM, et al. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood*. 1990;75(3):555-562.
9. Storb R, Deeg HJ, Pepe M, et al. Methotrexate and cyclosporine versus cyclosporine alone for prophylaxis of graft-versus-host disease in patients given HLA-identical marrow grafts for leukemia: long-term follow-up of a controlled trial. *Blood*. 1989;73(6):1729-1734.
10. Cutler C, Logan B, Nakamura R, et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. *Blood*. 2014;124(8):1372-1377.



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