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Is post-transplant cyclophosphamide a true game-changer in allogeneic transplantation: The struggle to unlearn

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ABSTRACT

Close HLA matching of donors and recipients has been the dogma for successful allogeneic blood or marrow transplantation (BMT), to limit the complications of graft rejection and graft-versus-host disease (GVHD). However, many patients in need, especially those in certain racial and ethnic groups such as African-Americans and Hispanics, are unable to find matches despite increased availability of unrelated donors. Unfortunately, despite many early attempts to develop safe, related haploidentical allogenic BMT, mortality rates exceeding 50% from severe GVHD led most centers to steer away from such transplants by the mid-1990s. However, recent advances based largely on the development of high-dose post-transplant cyclophosphamide GVHD prophylaxis, now yield results with haploidentical related donors that approach those with matched donors. With emerging data that younger donor age may be the most important donor selection criterion, HLA-mismatched donors may even have advantages over matched donors in certain situations. Although the exact role that haploidentical donors should play in donor selection strategies is still being defined, the lack of an HLA-matched donor should no longer ever be an exclusion for allogeneic BMT. Unfortunately, this progress in donor availability has not yet been fully recognized by the medical community. Such a discordance between new advances and their clinical translation highlights that changing standard practice is difficult and takes longer than it should, at least in part because it requires "unlearning" long-standing behaviors.

Historically, graft-versus-host disease (GVHD), particularly in the setting of HLA disparity, has constrained the applicability and availability of allogeneic blood or marrow transplantation (BMT). In fact, the search for appropriate alternative donors on behalf of the many potential BMT recipients lacking matched donors could be considered the "holy grail" of the BMT field. Even when a match can be identified, National Marrow Donor Program data indicate that a median of 4 months is required to complete searches that result in BMT. Thus, some patients will succumb to disease while awaiting identification of a suitable HLA-matched donor. Given that almost all patients will have a HLA-haploidentical related donor (ie, parent, sibling, child, niece, nephew, grandchild, or cousin), the ability to expeditiously and safely use such donors would open up allogeneic BMT to virtually all who might benefit. Haploidentical related BMT would be especially useful for certain ethnic groups, such as patients of African descent and Hispanics, in whom finding a matched unrelated donor has been problematic. Until recently, however, mortality rates exceeding 50% from severe GVHD have steered most centers away from the use of haploidentical related donors.

Early preclinical and clinical allogeneic BMT studies exclusively utilized total body irradiation (TBI), because of its dual anticancer and immunosuppressive properties. Due to limited access to facilities that could provide TBI at Johns Hopkins in the 1960's, as well as toxicity concerns, Santos and Owens explored potential new BMT conditioning agents by evaluating the immunosuppressive

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properties of the available anticancer agents. They found cyclophosphamide (Cy) to be the most immunosuppressive, and accordingly developed it as a replacement for TBI [1]. The first 48 patients receiving allogeneic BMT at Johns Hopkins received high-dose Cy as the sole conditioning regimen. At the same time, Santos and Owens also found that Cy, when used at high-doses on days 2–5 after transplantation, was highly effective in preventing alloreactivity in mice [2,3]. However, because of concerns at the time that high-dose Cy given after BMT might damage transplanted hematopoietic stem cells (HSCs), the clinical trials that arose from these preclinical studies actually used low-dose Cy as GVHD prophylaxis. A randomized trial at Hopkins eventually showed that cyclosporine was significantly better than low-dose Cy for GVHD prophylaxis [4].

Subsequently, laboratory as well as corroborating clinical data showed that HSCs are resistant to high-dose Cy [5]. HSCs highly express aldehyde dehydrogenase 1 (ALDH1), the body's primary means of inactivating Cy, while lymphocytes generally express low levels [5]. The primary function of ALDH1, also known as retinaldehyde dehydrogenase, is the biosynthesis of retinoic acid, which is required for the growth and differentiation of HSCs and other highly proliferative cells. Cy was actually rationally designed as an inactive prodrug that would selectively target cancer cells expressing phosphamidase capable of cleaving Cy's phosphoramide bond, releasing phosphoramide mustard; normal cells that were thought to express less phosphamidase would be relatively spared. Although an inactive prodrug, this hypothetical mechanism of action was ultimately proven incorrect. It took nearly a quarter century after Cy was FDA-approved in 1959, for Hilton and Colvin at Hopkins to dissect its actual metabolic pathway. The prodrug actually undergoes bioactivation by liver P450 enzymes to its active transport congeners, 4-hydroxyCy and aldophosphamide, which exist in tautomeric equilibrium. ALDH1 actually inactivates Cy by serendipity, through oxidation of the active metabolic aldehyde intermediate aldophosphamide to the inactive carboxylic acid carboxyphosphamide [5]. The success of high-dose Cy without HSC rescue as treatment for aplastic anemia and other autoimmune diseases at Hopkins [6] was further proof of its potent immunosuppressive, but HSC-sparing, properties.

This laboratory and clinical evidence of HSC resistance to Cy led to our group re-exploring it as GVHD prophylaxis, however this time at the high doses Santos and Owens found were most effective in animal models [2,3] but were unwilling to test clinically. High-dose Cy given early after BMT was again shown to effectively prevent alloreactivity (GVHD and graft rejection) and spare HSCs, allowing successful mismatched BMT in mice [7]. Translational clinical trials based on these preclinical studies showed that haploidentical related BMT using post-transplantation Cy (PTCy) produced outcomes similar to those seen with HLA-matched BMT [8]. Moreover, the degree of HLA disparity did not influence outcome as long as the donor was at least haploidentical [9], and outcomes were excellent even in patients in their 70's [10]. A national multi-institutional clinical trial through the BMT Clinical Trials Network (CTN) confirmed the safety and effectiveness of haploidentical BMT using PTCy [11]. Multiple studies, including large registry analyses, have now shown that haploidentical BMT with PTCy produces results similar to those seen with matched sibling and unrelated transplants [12–15]. Our group has recently shown that PTCy also allows safe and effective mismatched unrelated BMT, including up to 5/10 mismatches, with results similar to haploidentical BMT using PTCy [16].

In addition to controlling haploidentical alloreactivity, PTCy is associated with excellent immune reconstitution and a low incidence of severe opportunistic infections [8]. The timing of the PTCy appears to contribute to its selectivity toward alloreactive T cells. Early after allogeneic BMT, both donor and host alloreactive T cells are maximally activated and proliferative, while T cells specific for infectious agents are quiescent and thus less sensitive to Cy-mediated cytotoxicity. Recent data from our group demonstrate that memory lymphocytes, like other cells with substantial proliferative capacity, also highly express ALDH1 and are thus relatively resistant to Cy; these Cy-resistant cells undoubtedly also contribute to the favorable immune reconstitution after PTCy [17].

Allograft T cell depletion (TCD) can also limit GVHD after haploidentical related BMT. Although success with this approach has been reported in children, most trials in adults have been associated with relatively high non-relapse mortality (NRM) rates primarily as a result of slow immunologic reconstitution and infectious complications [18]. Ciurea et al. reported the first direct comparison between TCD and PTCy for haploidentical related BMT [19]. In a retrospective analysis of two cohorts of haploidentical BMT patients treated at MD Anderson using the same conditioning regimen, PTCy produced statistically superior actuarial overall and progression-free survivals when compared to TCD. Although both approaches were associated with low rates of GVHD, PTCy was associated with significantly improved immune reconstitution and lower NRM, predominately because of fewer infectious deaths.

In contrast to PTCy, TCD shows no selectivity toward alloreactive T cells, also eliminating T cells reactive against infectious agents as well as memory T cells. Thus, functional immune reconstitution after TCD can adequately develop in children and young adults from the thymic output of naïve T cells, but not in older adults (with thymic involution) who rely predominately on the peripheral expansion of memory T cells [20]. Transplantation with another alternative donor source, unrelated umbilical cord blood, also produces excellent results in children and young adults. However, immune reconstitution and infectious complications have also been concerns in older adults transplanted with these products that are similarly deficient in memory T cells [20]. A randomized trial comparing unrelated umbilical cord blood and haploidentical related transplantation in adults lacking matched donors through the BMT CTN has just ended and results are pending. Regardless of the results of this trial, PTCy now allows safe and effective mismatched donor BMT such that no patient in need of allogeneic BMT should ever be denied the procedure for lack of a matched donor option. Moreover, the successful development of PTCy would not have been possible without the integrated work of a team of laboratory and clinical scientists with broad expertise in transplantation biology, pharmacology, hematopoiesis, and immunology.

However, although recent data suggest that partially mismatched allogeneic BMT using PTCy yields results similar to those with matched donors [12–15], this progress has not yet been fully recognized by the medical community. Such a discordance between new findings and their clinical translation is consistent with recent evidence demonstrating that changing standard practice is difficult and takes longer than it should, at least in part because it requires “unlearning” long-standing behaviors [21,22]. Accordingly, the recently updated 2017 European LeukemiaNet treatment guidelines list only matched donor transplantation as standard consolidation for AML with adverse-risk genetics [23]. Moreover, despite reports of the universal availability and safety of related

haploidentical BMT for sickle cell disease [24,25], recent articles reviewing novel therapies for this disease continue to comment on the limited availability of donors [26,27]. It is even feasible that the advantages afforded by partially matched related donors, such as donor availability, the ability to choose young donors, and control over allograft quality, could eventually make them preferred over matched donors. These potential benefits are particularly promising for ethnic groups underserved by unrelated registries. In fact, results using related haploidentical donors already suggest that allogeneic BMT should no longer be considered a treatment that is available to only the small fraction of SCD patients with matched donors. Hopefully, the process of "unlearning" [21,22] the long-standing convention of an absolute need for matched donors in alloBMT will soon be realized.

Declaration of competing interest

The authors declare no competing financial interests.

References

[1] Owens Jr. AH, Santos GW. The induction of graft versus host disease in mice treated with cyclophosphamide. J Exp Med 1968;128:277–91.
[2] Santos GW, Owens AH. Production of graft-versus-host disease in the rat and its treatment with cytotoxic agents. Nature 1966;210:139–40.
[3] Owens AH, Santos GW. The effect of cytotoxic drugs on graft-versus-host disease in mice. Transplantation 1971;11:378–82.
[4] Santos GW, Tutschka PJ, Brookmeyer R, et al. Cyclosporine plus methylprednisolone versus cyclophosphamide plus methylprednisolone as prophylaxis for graft-versus-host disease: a randomized double-blind study in patients undergoing allogeneic marrow transplantation. Clin Transpl 1987;1:21–8.
[5] Emadi A, Jones RJ, Brodsky RA. Cyclophosphamide and cancer: golden anniversary. Nat Rev Clin Oncol 2009;6:638–47.
[6] Dezern AE, Petri M, Drachman DB, Kerr D, Hammond ER, Kowalski J, et al. High-dose cyclophosphamide without stem cell rescue in 207 patients with aplastic anemia and other autoimmune diseases. Medicine (Baltim) 2011;90:89–98.
[7] 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;98:3456–64.
[8] Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant 2008;14:641–50.
[9] Kasamon YL, Luznik L, Leffell MS, Kowalski J, Tsai HL, Bolanos-Meade J, Morris LE, Crilley PA, O'Donnell PV, Rossiter N, Huff CA, Brodsky RA, Matsui WH, Swinnen LJ, Borrello I, Powell JD, Ambinder RF, Jones RJ, Fuchs EJ. Nonmyeloablative HLA-haploidentical bone marrow transplantation with high-dose posttransplantation cyclophosphamide: effect of HLA disparity on outcome. Biol Blood Marrow Transplant 2010;16:482–9.
[10] Kasamon YL, Bolanos-Meade J, Prince GT, Tsai HL, McCurdy SR, Kanakry JA, Rosner GL, Brodsky RA, Perica K, Smith BD, Gladstone DE, Swinnen LJ, Showel MM, Matsui WH, Huff CA, Borrello I, Pratz KW, Mcdevitt MA, Gojo I, Dezern AE, Shanbhag S, Levis MJ, Luznik L, Ambinder RF, Fuchs EJ, Jones RJ. Outcomes of nonmyeloablative HLA-haploidentical blood or marrow transplantation with high-dose post-transplantation cyclophosphamide in older adults. J Clin Oncol 2015;33:3152–6.
[11] Brunstein CG, Fuchs EJ, Carter SL, Karanes C, Costa LJ, Wu J, et al. Alternative donor transplantation after reduced intensity donditioning: results of parallel phase II trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. Blood 2011;118:282–8.
[12] McCurdy SR, Kanakry JA, Showel MM, Tsai HL, Bolanos-Meade J, Rosner GL, Kanakry CG, Perica K, Symons HJ, Brodsky RA, Gladstone DE, Huff CA, Pratz KW, Prince GT, Dezern AE, Gojo I, Matsui WH, Borrello I, Mcdevitt MA, Swinnen LJ, Smith BD, Levis MJ, Ambinder RF, Luznik L, Jones RJ, Fuchs EJ, Kasamon YL. Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide. Blood 2015;125:3024–31.
[13] Ciurea SO, Zhang MJ, Bacigalupo AA, Bashey A, Appelbaum FR, Aljitawi OS, Armand P, Antin JH, Chen J, Devine SM, Fowler DH, Luznik L, Nakamura R, O'Donnell PV, Perales MA, Pingali SR, Porter DL, Riches MR, Ringden OT, Rocha V, Vij R, Weisdorf DJ, Champlin RE, Horowitz MM, Fuchs EJ, Eapen M. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood 2015;126:1033–40.
[14] Kanate AS, Mussetti A, Kharfan-Dabaja MA, Ahn KW, DiGilio A, Beitinjaneh A, Chhabra S, Fenske TS, Freytes C, Gale RP, Ganguly S, Hertzberg M, Klyuchnikov E, Lazarus HM, Olsson R, Perales MA, Rezvani A, Riches M, Saad A, Slavin S, Smith SM, Sureda A, Yared J, Ciurea S, Armand P, Salit R, Bolanos-Meade J, Hamadani M. Reduced-intensity transplantation for lymphomas using haploidentical related donors vs HLA-matched unrelated donors. Blood 2016;127:938–47.
[15] Ghosh N, Karmali R, Rocha V, Ahn KW, DiGilio A, Hari PN, Bachanova V, Bacher U, Dahi P, de LM, D'Souza A, Fenske TS, Ganguly S, Kharfan-Dabaja MA, Prestidge TD, Savani BN, Smith SM, Sureda AM, Waller EK, Jaglowski S, Herrera AF, Armand P, Salit RB, Wagner-Johnston ND, Fuchs E, Bolanos-Meade J, Hamadani M. Reduced-Intensity transplantation for lymphomas using haploidentical related donors versus HLA-matched sibling donors: a center for international blood and marrow transplant research analysis. J Clin Oncol 2016;34:3141–9.
[16] Kasamon YL, Ambinder RF, Fuchs EJ, Zahurak M, Rosner GL, Bolanos-Meade J, Levis MJ, Gladstone DE, Huff CA, Swinnen LJ, Matsui WH, Brodsky RA, Borrello I, Jones RJ, Luznik L. Prospective study of nonmyeloablative, HLA-mismatched unrelated BMT with high-dose posttransplantation cyclophosphamide. Blood Adv 2017;1:288–92.
[17] Kanakry CG, Ganguly S, Zahurak M, Bolanos-Meade J, Thoburn C, Perkins B, Fuchs EJ, Jones RJ, Hess AD, Luznik L. Aldehyde dehydrogenase expression drives human regulatory T cell resistance to posttransplantation cyclophosphamide. Sci Transl Med 2013;5:211ra157.
[18] Ciceri F, Labopin M, Aversa F, Rowe JM, Bunjes D, Lewalle P, et al. A survey of fully haploidentical hematopoietic stem cell transplantation in adults with high-risk acute leukemia: a risk factor analysis of outcomes for patients in remission at transplantation. Blood 2008;112:3574–81.
[19] Ciurea SO, Mulanovich V, Saliba RM, Bayraktar UD, Jiang Y, Bassett R, Wang SA, Konopleva M, Fernandez-Vina M, Montes N, Bosque D, Chen J, Rondon G, Alatrash G, Alousi A, Bashir Q, Korbling M, Qazilbash M, Parmar S, Shpall E, Nieto Y, Hosing C, Kebriaei P, Khouri I, Popat U, de LM, Champlin RE. Improved early outcomes using a T cell replete graft compared with T cell depleted haploidentical hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2012;18:1835–44.
[20] Seggewiss R, Einsele H. Immune reconstitution after allogeneic transplantation and expanding options for immunomodulation: an update. Blood 2010;115:3861–8.
[21] Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med 2011;104:510–20.
[22] Gupta DM, Boland Jr. RJ, Aron DC. The physician's experience of changing clinical practice: a struggle to unlearn. Implement Sci 2017;12:28–0555.
[23] Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(424–44):424–44.
[24] de la Fuente J, Dhedin N, Koyama T, Bernaudin F, Kuentz M, Karnik L, Soci G, Culos Robert A, Brodsky RA, Michael R, DeBaun MR, Kassim AA. Haploidentical bone marrow transplantation with post-transplantation cyclophosphamide plus thiotepa improves donor engraftment in patients with sickle cell anemia: results of an international learning collaborative. Biol Blood Marrow Transplant 2019;25:1197–209.
[25] Bolaños-Meade J, Cooke KR, Gamper CJ, Ali SA, Ambinder RF, Borrello IM, Fuchs EJ, Gladstone DE, Gocke CB, Huff CA, Luznik L, Swinnen LJ, Symons HJ, Terezakis SA, Wagner-Johnston N, Jones RJ, Brodsky RA. Effect of increased dose of total body irradiation on graft failure associated with HLA-haploidentical transplantation in patients with severe haemoglobinopathies: a prospective clinical trial. Lancet Haematol 2019;6:e183–93.
[26] Cai L, Bai H, Mahairaki V, et al. A universal approach to correct various HBB gene mutations in human stem cells for gene therapy of beta-thalassemia and sickle cell disease. Stem Cells Transl Med 2018;7:87–97.
[27] Ataga KI, Stocker J. The trials and hopes for drug development in sickle cell disease. Br J Haematol 2015;170:768–80.