Brief Report

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TRANSPLANTATION

Low immunosuppressive burden after HLA-matched related or unrelated BMT using posttransplantation cyclophosphamide

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Key Points

- After PTCy, ~50% of MRD alloBMT patients and ~30% of MUD alloBMT patients required no additional systemic immunosuppression.
- By 1-year posttransplant, the vast majority of patients had permanently discontinued all systemic immunosuppression.

The intensive and prolonged immunosuppressive therapy required to prevent or treat graft-versus-host disease (GVHD) after allogeneic blood or marrow transplantation (alloBMT) puts patients at substantial risk for life-threatening infections, organ toxicity, and disease relapse. Posttransplantation cyclophosphamide (PTCy) can function as single-agent GVHD prophylaxis after myeloablative, HLA-matched related (MRD), or HLA-matched unrelated (MUD) donor T-cell–replete bone marrow allografting, obviating the need for additional prophylactic immunosuppression. However, patients who develop GVHD require supplemental treatment. We assessed the longitudinal requirement for immunosuppressive therapy in 339 patients treated with this transplantation platform: 247 receiving busulfan/cyclophosphamide (BuCy) conditioning (data collected retrospectively) and 92 receiving busulfan/fludarabine (BuFlu) conditioning (data collected prospectively). Approximately 50% of MRD patients and 30% of MUD patients never required immunosuppression beyond PTCy. In patients requiring further immunosuppression, typically only 1 to 2 agents were required, and the median durations of systemic pharmacologic immunosuppression for the BuCy MRD, BuFlu MRD, BuCy MUD, and BuFlu MUD groups all were 4.5 to 5 months. For these 4 groups, 1-year probabilities of being alive and off all systemic immunosuppression were 61%, 53%, 53%, and 51% and 3-year probabilities were 53%, 48%, 49%, and 56%, respectively. These data suggest that PTCy minimizes the global immunosuppressive burden experienced by patients undergoing HLA-matched alloBMT. (*Blood*. 2017;129(10):1389-1393)

Introduction

Standard graft-versus-host disease (GVHD) prophylaxis after allogeneic blood or marrow transplantation (alloBMT) consists of short-course methotrexate (MTX) followed by 3 to 6 months of a calcineurin inhibitor (CNI).[1] However, most patients require more intensive and prolonged immunosuppressive therapy to treat GVHD when it occurs. In 1 study, 89% of patients treated with CNI-based GVHD prophylaxis after myeloablative conditioning (MAC) for HLA-matched alloBMT required corticosteroids, with the majority continually requiring corticosteroids and at least 1 other immunosuppressive agent throughout the first posttransplant year.[2] Few patients receiving MAC were able to discontinue immunosuppression within the first 20 months.[2] The intensity and duration of this immunosuppression puts patients at substantial risk for potentially life-threatening infections,[3-5] can have significant end-organ toxicity, may increase the risk of relapse,[6] and obstructs the implementation of emerging immunotherapeutic strategies to prevent or treat relapse. Thus, it has been proposed that the primary measure of success for GVHD prevention studies should be the need for systemic immunosuppression for GVHD treatment.[7]

Posttransplantation cyclophosphamide (PTCy) is a promising therapy for reducing GVHD incidence and immunosuppression use.[8] When used after MAC and HLA-matched bone marrow allografting, PTCy is effective as single-agent GVHD prophylaxis[9-12]; no immunosuppression is routinely administered after posttransplant day +4 in patients not experiencing GVHD. In this study, utilizing immunosuppression data from 339 patients treated with this transplantation platform, we tested the hypothesis that the global immunosuppressive burden experienced by PTCy-treated patients would compare favorably with published data using CNI-based GVHD prophylaxis.

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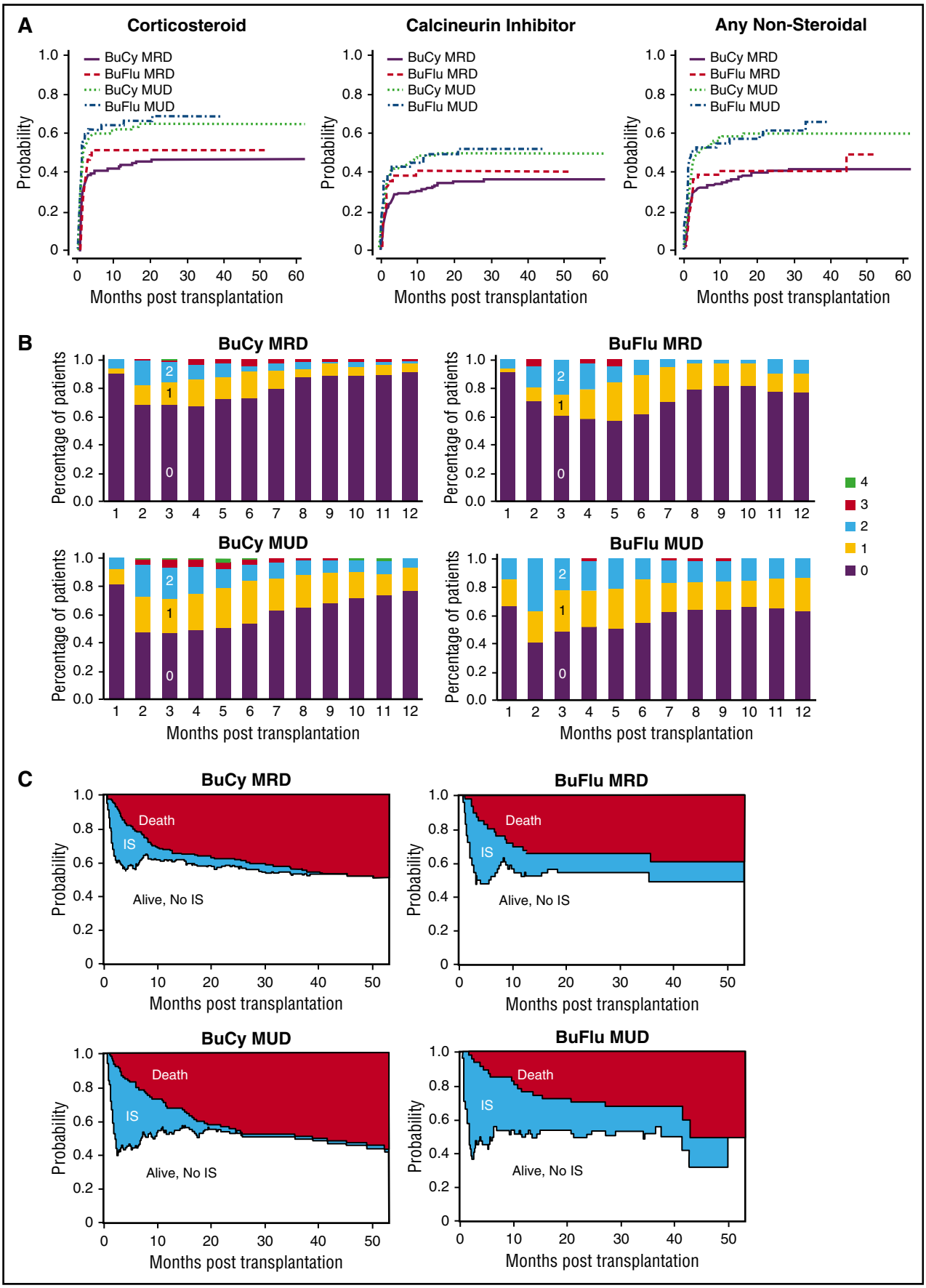

Figure 1.

Table 1. Rates of GVHD and immunosuppression use

	BuCy MRD	BuFlu MRD	BuCy MUD	BuFlu MUD
GVHD				
Cumulative incidences of acute GVHD at 1 y, % (95% CI)				
Grade II-IV	40 (32-47)	42 (28-56)	54 (43-63)	60 (44-72)
Grade III-IV	12 (8-18)	13 (5-25)	15 (9-23)	19 (9-32)
Cumulative incidences of chronic GVHD at 2 y, % (95% CI)	6.5 (3-11)	6.7 (2-17)	9.7 (5-17)	21 (11-34)
Immunosuppression				
Cumulative incidences of initiation by 3 y, % (95% CI)				
Corticosteroid	46 (38-54)	51 (36-65)	65 (54-73)	68 (53-80)
Any nonsteroidal immunosuppressant	40 (32-48)	40 (26-54)	58 (47-67)	64 (47-77)
CNI	36 (28-44)	40 (26-54)	50 (39-59)	51 (36-65)
Never required IS beyond PTCy, %				
All patients	51	47	31	26
Patients alive at last follow-up	49	50	24	30
Duration of IS in those requiring IS beyond PTCy, median (IQR), d				
Corticosteroid	57 (40-99)	74 (41-206)	63 (46-133)	147 (49-481)
Any nonsteroidal IS	141 (55-218)	151 (53-354)	162 (64-254)	232 (87-561)
Pharmacologic	142 (77-190)	147 (78-231)	158 (70-281)	149 (69-264)
CNI	135 (79-175)	147 (78-231)	156 (67-281)	145 (62-278)
Phototherapeutic	45 (28-109)	225 (146-262)	113 (64-148)	612 (281-738)
Probability of being alive and off IS, %				
At 1 y	61	53	53	51
At 3 y	53	48	49	56

Note: The percentages of patients not requiring immunosuppression were calculated using the numbers of patients within a group who did not use immunosuppression beyond PTCy as the numerators and either all patients in that group or patients in that group alive at last follow-up as the denominators. The probabilities of being alive and off immunosuppression were calculated from the multistate models (Figure 1C).

CI, confidence interval; IQR, interquartile range; IS, immunosuppression.

Study design

Patients

All patients received PTCy as single-agent GVHD prophylaxis after MAC and HLA-matched related (MRD) or HLA-matched unrelated (MUD) donor T-cell–replete bone marrow transplantation. Details of the treatment regimens are included in the supplemental Methods (see supplemental Data, available on the *Blood* Web site). The first cohort included all 247 patients treated from 2004 to 2011 at Johns Hopkins Hospital with busulfan/cyclophosphamide (BuCy) MAC (supplemental Table 1)[9,10]; data were collected retrospectively after institutional review board (IRB) approval. The second cohort included all 92 patients treated from 2009 to 2011 on an IRB-approved, multi-institutional study using busulfan/fludarabine (BuFlu) MAC (supplemental Table 1)[11]; data were collected prospectively as immunosuppression use was a predefined secondary end point of the study. Median follow-up was 4.5 and 2.9 years, respectively, based on the reverse Kaplan-Meier method. Given higher GVHD incidences after MUD compared with MRD allografting for this transplantation platform,[10,11] immunosuppression use was stratified by donor type.

Definitions

To assess the total immunosuppressive burden associated with this transplantation platform, included was any systemic pharmacologic or phototherapeutic agent given posttransplant for any reason other than corticosteroids at physiologic replacement dosing for documented adrenal insufficiency (supplemental Table 2). This assessment encompassed treatment of GVHD or engraftment syndrome, treatment of GVHD after donor lymphocyte infusion (DLI) or second alloBMT, or GVHD prophylaxis for second alloBMT (supplemental Table 3). Thus, the only competing risk for immunosuppression was death. The duration of each immunosuppressive agent was the entire length of time between the day of initiation and the last day received prior to permanent discontinuation. The only exception was for treatment gaps of >3 months in which case the durations of the discontinuous blocks were summed. Topical agents or budesonide were not included in these analyses. Acute and chronic GVHD were diagnosed and graded based on standard criteria.[13,14] Competing risks for GVHD were graft failure, relapse, DLI, and death.

Statistical analysis

Cumulative incidences were estimated using a competing-risk framework. Multistate models and the Aalen-Johansen estimator were used to estimate the probabilities of existing in 1 of 3 states at any given time: (1) alive, not on immunosuppression, (2) alive, on immunosuppression, or (3) death (absorbing state) (supplemental Figure 1).[15,16] All analyses were performed using R version 3.3.0.

Results and discussion

Cumulative incidences are shown for acute and chronic GVHD (Table 1) and initiation of immunosuppression (Figure 1A; Table 1).

Figure 1. Global burden of immunosuppression. (A) The cumulative incidences of initiation of a corticosteroid (left panel), CNI (center panel), or any nonsteroidal systemic pharmacologic or phototherapeutic immunosuppressant agent including a CNI (right panel) are shown for each of the 4 groups: BuCy conditioning with MRD allografting, BuFlu conditioning with MRD allografting, BuCy conditioning with MUD allografting, and BuFlu conditioning with MUD allografting. These analyses included immunosuppression (IS) use for any reason including treatment of acute or chronic GVHD, treatment of engraftment syndrome, treatment of GVHD occurring after DLI or second allogenic transplant, and prophylaxis for second allogeneic transplant in those requiring it for graft failure or relapsed disease. The only competing risk for these cumulative incidence curves was death. (B) The number of immunosuppressive agents with which each patient was being treated at the end of each 30-day interval is shown throughout the first posttransplant year for each of the 4 groups. No patients ever required >4 agents simultaneously. (C) For each of the 4 groups, multistate modeling shows the instantaneous probability of being in 1 of 3 states: (1) alive, not on immunosuppression (Alive, No IS), (2) alive, on immunosuppression (IS), or (3) dead (Death). All patients started in state 1 on day +5 of transplant after receiving cyclophosphamide 50 mg/kg per day on posttransplant days +3 and +4. Patients could transition between the states of being alive and on or off immunosuppression, but death was an absorbing state.

Ten percent of corticosteroid initiation and 17% of nonsteroidal immunosuppression initiation occurred after DLI or second alloBMT (supplemental Table 3). Approximately 50% of MRD alloBMT patients and 30% of MUD alloBMT patients never required immunosuppression beyond PTCy on days +3 and +4 (Table 1). When immunosuppression was required, it was typically limited to 1 to 2 agents (Figure 1B). Importantly, the median durations of pharmacologic immunosuppression (4.5-5 months for all groups) (Table 1) were shorter than would typically be given prophylactically (6 months) for patients treated with CNI-based GVHD prophylaxis.

Multistate modeling was used to assess the longitudinal immunosuppressive burden. In all groups, >40% to 50% of patients were alive and off immunosuppression throughout follow-up. Not unexpectedly, the immunosuppressive burden was greatest within the first posttransplant year. After that point, few patients remained on immunosuppression (Figure 1C; Table 1).

Our study included 2 cohorts, including 1 in which data were collected prospectively. Despite differences in conditioning and timing of data collection, we observed very similar results across cohorts in the percentages of patients who never required additional immunosuppression and the patterns of immunosuppression use in those who did. The major difference was that the durations of steroids and phototherapeutic agents, but not nonsteroidal pharmacologic agents, were higher for BuFlu MUD compared with BuCy MUD patients. This higher immunosuppressive burden likely is due in part to slightly higher rates of grade III-IV acute GVHD and chronic GVHD in that group, which may in part be attributable to higher rates of female-into-male-donor allografting (23% vs 9%; supplemental Table 1).[17,18] These results also may have been skewed by the protracted use of extracorporeal photopheresis in a limited number of BuFlu patients.

Our results only apply to patients receiving bone marrow allografts. PTCy may be insufficient as single-agent GVHD prophylaxis for HLA-matched peripheral blood stem cell transplantation due to high rates of grade III-IV acute GVHD,[19,20] although adding a CNI or sirolimus to PTCy appears effective.[21,22]

Despite low incidence of chronic GVHD, relapse rates in our patients are acceptable (supplemental Figure 2). Indeed, they appear similar to relapse rates reported in other recent studies (supplemental Figure 2; Table 3 of Kanakry et al[10]).

The global immunosuppressive burden in our patients compares favorably with CNI-based GVHD prophylaxis with or without antithymocyte globulin (ATG). In a randomized phase 3 study of myeloablative MUD alloBMT using cyclosporine/MTX ± ATG-Fresenius,[23] the 3-year probabilities of being alive and immunosuppression-free were 53% for ATG-Fresenius–treated patients and 17% for patients not receiving ATG-Fresenius.[23] Our results are similar to the ATG-Fresenius–treated patients. Results for ATG were not as encouraging in a randomized phase 3 study using a different formulation (thymoglobulin).[24] Although the primary end point of freedom from immunosuppression at 1-year posttransplant statistically favored the thymoglobulin group (37% vs 16%), these absolute probabilities were markedly lower than the ATG-Fresenius–treated patients or our own patients. Additionally, the benefit of thymoglobulin was not seen in patients receiving bone marrow allografts.[24] In the randomized phase 3 study of MRD alloBMT using CNI-based GVHD prophylaxis ± ATG-Fresenius, rates of cyclosporine discontinuation by 1 year were 91% and 39%, respectively.[25] This result for the ATG-Fresenius group is very similar to our MRD patients. However, given that half of our MRD patients required no additional immunosuppression after day +4, the immunosuppressive burden during the first posttransplant year favors PTCy. Overall, these results provide sufficient clinical equipoise to support a study comparing PTCy vs ATG for minimizing GVHD and the posttransplant immunosuppressive burden after HLA-matched alloBMT. These data also furnish benchmarks against which to compare results from the ongoing BMT Clinical Trials Network 1301 study comparing PTCy vs ex vivo T-cell depletion for HLA-matched alloBMT.

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Authorship

Contribution: C.G.K. and L.L. designed the study; J.B.-M., Y.L.K., M. Mielcarek, K.R.C., R.F.A., E.J.F., P.V.O., and R.J.J. contributed to the study design; C.G.K., J.B.-M., N.D., T.F., and M. Medeot collected data; Y.L.K., I.G., B.D.S., and J.A.K. performed blinded assessments of the remission status of patients at transplant; C.G.K. assembled data; C.G.K., J.B.-M., Y.L.K., T.F., M. Mielcarek, I.G., B.D.S., J.A.K., I.M.B., R.A.B., D.E.G., C.A.H., W.H.M., L.J.S., R.F.A., E.J.F., M.J.d.L., B.S.A., P.V.O., R.J.J., and L.L. provided clinical care of patients; M.Z. and R.V. performed statistical analyses; C.G.K., M.Z., and R.V. prepared figures; C.G.K. and L.L. wrote the manuscript; and all authors edited the manuscript.

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