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Bone Marrow Transplant. Author manuscript; available in PMC 2021 July 14.

Published in final edited form as:

Bone Marrow Transplant. 2020 April ; 55(4): 758–762. doi:10.1038/s41409-019-0725-8.

Post-transplant cyclophosphamide in allogeneic bone marrow transplantation for the treatment of non-malignant hematological diseases

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Abstract

We present a single-center retrospective series of allogeneic bone marrow transplantation (BMT) with the use of post-transplant cyclophosphamide (PTCy) in the setting of non-malignant hematological conditions. Nine patients were treated between 2013 to 2019. Non-myeloablative conditioning consisted of anti-thymocyte globulin, fludarabine, low-dose cyclophosphamide and total body irradiation (200 cGy) followed by allogeneic bone marrow infusion. Post-BMT GVHD prophylaxis was with PTCy, tacrolimus and mycophenolate mofetil. At a median follow-up of 24 months (range 4, 63), all patients are alive, with donor-derived hematopoiesis and free of significant acute or chronic GVHD. Donors were haploidentical (n=6), fully matched unrelated (n=2), and fully matched sibling (n=1). Neutrophil and platelet engraftment occurred at a median of 21 days and 33 days, respectively, after transplantation. Three patients (3/9, 33%) experienced stage 1–2 acute skin GVHD. The only cases of chronic GVHD are in 3 patients (3/9, 33%) with ocular disease (two mild, one moderate). No patient has required systemic immunosuppression beyond 12 months after BMT. PTCy based non-myeloablative allogeneic BMT is safe and effective for non-malignant hematologic conditions and should be prospectively compared to historical regimens.

Introduction

While aplastic anemia (AA) was historically a disease with a low survival rate, the advent of effective immunosuppressive therapy and allogeneic bone marrow transplantation (BMT) have dramatically improved the prognosis. Now, over 50 years old, the first publication describing allogeneic BMT for severe aplastic anemia revealed a mortality rate of over 50% in the first 100 days for this early small cohort of 24 patients.(1) Subsequently, significant improvements in conditioning regimens, HLA matching, and appropriate risk stratification of therapy have led to dramatic improvements in outcomes.(2) Due to a continued risk of disease recurrence and secondary myelodysplastic syndrome or acute leukemia with

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The authors report no relevant competing interests.

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traditional immunosuppressive therapy, along with continued advancements in transplantation care, there is an emerging trend to proceed directly with allogeneic transplantation as initial therapy for patients with AA.(3) Allogeneic transplantation approaches for patients with other non-malignant hematological conditions including Diamond-Blackfan Anemia (DBA) and paroxysmal nocturnal hemoglobinuria (PNH) have been traditionally extrapolated from approaches used for patients with AA even with a clear difference in underlying pathophysiology.(4)

Popularized by investigators at Johns Hopkins University (JHU), post transplantation cyclophosphamide (PTCy) after HLA-haploidentical BMT has been shown to facilitate successful donor engraftment and yield rates of acute and chronic GVHD comparable to or less than that historically observed with matched sibling transplant procedures.(5–7) PTCy is also being increasingly used in the setting of conventional matched related or unrelated donor transplants with similar efficacy.(8) Augmented protection against GVHD is especially useful in non-malignant conditions where a graft versus host effect is only harmful.(9, 10) Recent results from a small single center, JHU phase II clinical trial of mismatched donor allogeneic bone marrow transplantation with PTCy in refractory AA revealed excellent outcomes with a low risk of GVHD.(11)

Based on these findings, our institution has recently taken the approach of using a PTCy-based platform for allogeneic transplantation of patients with non-malignant hematologic conditions, especially those who lack a matched sibling donor. We present the results of 9 consecutive patients treated at our institution with this approach.

Methods

Patients

Patients underwent allogeneic transplantation between 2013–2019 at Massachusetts General Hospital Cancer Center. All patients included in the series were diagnosed with non-malignant hematologic conditions including AA (n=6), DBA (n=2), and PNH (n=1). This retrospective study was approved by the Dana-Farber Harvard Cancer Center (DFHCC) institutional review board.

Conditioning and GVHD prophylaxis

Rabbit anti-thymocyte globulin (ATG) was administered at 0.5mg/kg IV on day −9 and 2mg/kg IV on days −8 and −7. ATG was omitted from conditioning in one patient with DBA. Fludarabine was given at 30mg/m^2 IV daily from day −6 to day −2 (total dose 150 mg/m^2). Cyclophosphamide was given at 14.5mg/kg IV daily (day −6 and −5). 200 cGy of total body irradiation was given on day −1. Allogeneic bone marrow graft was infused on day 0. Post-transplant high-dose cyclophosphamide was given at 50mg/kg/day IV on days +3 and +4 with standard hydration and MESNA support. Mycophenolate mofetil (MMF) was administered at 15 mg/kg 3 times daily (maximum daily dose 3000 mg) starting on day +5 with taper beginning at day +35 to be stopped around day +100. Tacrolimus was started on day +5 with a target trough of 5–10 ng/mL with tapering beginning at day +180 with a goal to discontinue around day +360 in the absence of any significant GVHD.

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Supportive Care

Granulocyte colony-stimulating factor (G-CSF) was given starting day +5 at 5mcg/kg/day subcutaneously until neutrophil recovery. Blood products were administered per clinician discretion with standard transfusion thresholds of a platelet count $<10 \times 10^3/mm^3$ and a hemoglobin of < 7 g/dL. Patients received *Pneumocystis juroveci* prophylaxis starting by day +30 after transplant for a minimum of one year. Anti-herpes virus and varicella prophylaxis was administered for at least two years after BMT. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were monitored weekly after transplant and treated preemptively.

Engraftment and GVHD

Neutrophil engraftment was defined as the first day of an absolute neutrophil count >500/μl on three consecutive measurements. Platelet engraftment was defined as a platelet count >50,000/μl for at least seven days without transfusion support. Acute GVHD was graded by consensus grading criteria of the Mt. Sinai International GVHD Consortium (MAGIC).(12) Chronic GVHD was graded according to National Institutes of Health (NIH) consensus criteria.(13)

Results

Patients and Donors

Between December 2013 and April 2019, 9 patients with non-malignant hematologic conditions underwent BMT using this regimen (Table 1). The median age at the time of transplantation was 44 (range 24–73) years and 3 of 9 recipients were female. Median Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) was 0 (range 0–5).(14) The median donor age was 31 (range 22–53). The donors for 6 patients were haploidentical relatives, two donors were fully matched and unrelated, and one donor was a fully matched sibling. Bone marrow grafts were used for all patients.

Engraftment

Donor marrow grafts had a median $CD34^+$ cell count of 4.77×10^6/kg recipient ideal body weight (range 1.54×10^6 to 20.5×10^6). Median times to neutrophil and platelet engraftment were 21 days (range 16–27) and 31 days (range 23–57), respectively.

Outcomes

With a median follow up of 24 months (range 4–63) all patients are alive. There were no cases of overall grade II-IV acute GVHD. Three patients (3/9, 33%) experienced stage 1–2 acute skin GVHD. Three patients have developed chronic ocular GVHD (2 mild, 1 moderate), none of whom have required systemic immunosuppression. All six patients who are more than twelve months after transplant are free from systemic immunosuppression.

Three patients experienced CMV reactivation (of four donor/recipient pairs with either party being seropositive), two required preemptive therapy with oral valganciclovir, while the third had a single positive low level positive CMV PCR that resolved spontaneously. Three patients had low level positive EBV viremia, none of whom required pre-emptive treatment, and no cases of post-transplant lymphoproliferative disease have been observed. Other

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significant infectious complications before day +100 are listed in Table 1 and included BK cystitis in three patients, influenza, adenovirus cystitis, clostridium difficile colitis, streptococcal and enterococcal polymicrobial endocarditis and enterococcal bacteremia. Notably all three serious bacterial infections occurred in SAA patients, two of which had ANC's below 500/μl prior to conditioning therapy.

One patient developed engraftment syndrome which resolved quickly with systemic corticosteroids. Another patient suffered a small spontaneous subdural hemorrhage on day +10 after transplantation, but subseque ntly made a full neurologic recovery.

Discussion

Allogeneic transplantation has become increasingly successful for patients with non-malignant hematological diseases, allowing extension of such an approach to be considered earlier in the disease course. The emergence of PTCy-based regimens has allowed haploidentical donor transplantation to become a standard of care for patients with hematological malignancies, making allogenic transplantation a viable option for a much larger number of individuals. Increasingly, PTCy-based regimens are also being applied to transplants using fully matched related and unrelated donors through ongoing prospective studies. The low incidences of acute and chronic GVHD make this an especially attractive approach for non-malignant diseases, allowing consideration of earlier use of alternative donors including both unrelated and haploidentical. Here, we report our single center experience utilizing a PTCy-based BMT platform for 9 consecutive patients with non-malignant hematological conditions, 8 of whom received grafts from alternative donors, illustrating successful donor engraftment, lack of early toxicity and excellent long-term prevention of GVHD.

Initial attempts using alternative donor BMT for patients with severe AA resulted in mortality rates of nearly 90% for grafts mismatched at more than one HLA-locus and 75% for single locus HLA mismatch in the era prior to the routine use of ATG.(15) Not surprisingly, a retrospective analysis of pediatric and young adult patients with severe AA who underwent HCT between 1989–2003 with a variety of conditioning regimens and GVHD prophylaxis strategies found a survival benefit when using HLA-matched compared to HLA-mismatched grafts (5 year survival 57% and 39%, respectively).(16) Subsequently, an analysis from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry in patients with non-malignant disorders who underwent unrelated donor transplants between 1995 and 2007 (also with variable conditioning and GVHD prophylaxis strategies) confirmed a progressive increase in overall mortality and graft failure with degree of HLA mismatch.(17) Finally, in a study designed to determine the optimal ATG, cyclophosphamide and TBI conditioning regimen in patients who had failed medical therapy for severe AA, inferior survival was observed for recipients who received grafts from HLA-mismatched donors.(18)

The success of haploidentical donor transplantation for hematologic malignancies using PTCy-based regimens has gradually led to consideration of haploidentical donors for non-malignant conditions.(19) In a recent review, the outcomes of 277 patients with severe AA

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undergoing haploidentical transplantation were reported from eight studies. In five of the eight studies, ATG was used as part of GVHD prophylaxis, and PTCy-based regimens were used in two.(20) Across all studies, the incidence of grade 2–4 GVHD was only 12% and 1-year overall survival was 85%. A recent registry study of 158 Chinese adult and pediatric patients with severe AA compared those who underwent upfront transplantation from either an HLA matched sibling or haploidentical family member. Conditioning consisted of cyclophosphamide, ATG, and busulfan or fludarabine with cyclosporine, methotrexate, and MMF as GVHD prophylaxis. The authors found an increase in grade II-IV acute GVHD (30% vs 1.5%) and chronic GVHD (39% vs 8%) among those who received haploidentical transplants.(21) In another Chinese retrospective study of haploidentical donor transplantation for severe AA using cyclosporine, methotrexate, and MMF based GVHD prophylaxis, grade II-IV acute GVHD occurred in 20% of patients, cGVHD in 18%, and six of fifty-one patients died of transplant related complications.(22) Most recently, colleagues from JHU reported on their experience pioneering the conditioning and GVHD regimen we adopted in this report, in 16 patients with severe AA undergoing alternative donor BMT. Significant acute and chronic GVHD were rare and all patients were alive and off immunosuppressive therapy at last follow up.(11)

Historically, allogeneic transplantation for severe AA has typically been limited to younger patients with severe disease who had matched sibling donors or other patients who had failed initial medical therapy. CIBMTR data had supported these consensus recommendations, showing that in patients who received matched sibling allografts, survival correlated with age with 82% long-term survival in patients 1–20 years old, 72% in patients between 21–40, and 53% in patients over the age of 40.(23) These results were corroborated by an analysis of the European Group for Blood and Marrow Transplantation (EBMT) registry from 2001–2010.(24) Advancements in care, specifically, the advent of PTCy, has begun to challenge these guidelines,(25) and there is an increasing movement to utilize allogeneic transplantation for initial therapy, even with alternative donors (such as matched unrelated or haploidentical) and for older patients with limited comorbidities.(3) At Massachusetts General Hospital, given our albeit small but encouraging experience with non-myeloablative conditioning and PTCy-based GVHD prevention, we believe it is appropriate to consider up front transplantation, be it from a sibling, unrelated or haploidentical donor for all patients with severe AA who are fit to undergo BMT. We also believe that PTCy-based BMT should be an option for other non-malignant diseases for which BMT is indicated. While the pathophysiologic nature of these other non-malignant conditions are unique, they appear to respond just as well to this treatment platform as aplastic anemia and warrant further study. Although our series is limited in size, over half of the patients have two or more years of follow-up, and the lack of significant acute or chronic GVHD is compelling. This work contributes to the growing body of evidence suggesting that PTCy-based regimens for non-malignant hematologic diseases is exceptionally safe and results in minimal long-term complications, and may allow the application of allogeneic BMT to an increasing number of patients. Future studies should prospectively compare PTCy-based regimens to historically used regimens for non-malignant conditions.

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References

1. Storb R, Thomas ED, Buckner CD, Clift RA, Johnson FL, Fefer A, et al. Allogeneic Marrow Grafting for Treatment of Aplastic Anemia. Blood. 1974;43(2):157–80. [PubMed: 4149232]
2. Tolar J, Sodani P, Symons H. Alternative donor transplant of benign primary hematologic disorders. Bone Marrow Transplantation. 2015;50:619. [PubMed: 25665040]
3. Georges GE, Doney K, Storb R. Severe aplastic anemia: allogeneic bone marrow transplantation as first-line treatment. Blood Advances. 2018;2(15):2020–8. [PubMed: 30108110]
4. O'Boyle F, Bradshaw A, Szydlo RM, de la Fuente J. Haemopoietic Stem Cell Transplantation for Diamond Blackfan Anaemia Leads to Early and Sustained Engraftment with Good Long-Term Outcomes, but Has an Increased Risk of Gut Toxicity and Lung GvHD. Blood. 2016;128(22):2679-.
5. Kasamon YL, Bolaños-Meade J, Prince GT, Tsai H-L, McCurdy SR, Kanakry JA, et al. Outcomes of Nonmyeloablative HLA-Haploidentical Blood or Marrow Transplantation With High-Dose Post-Transplantation Cyclophosphamide in Older Adults. Journal of Clinical Oncology. 2015;33(28):3152–61. [PubMed: 26261255]
6. 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. Biology of Blood and Marrow Transplantation. 2008;14(6):641–50. [PubMed: 18489989]
7. Bachegowda LS, Shah MV, Veltri LW, Tanase A, Popat U, Anderlini P, et al. HLA-mismatched bone marrow transplantation in severe aplastic anemia. Bone Marrow Transplantation. 2017;52:1347. [PubMed: 28692030]
8. Bolaños-Meade J, Reshef R, Fraser R, Fei M, Abhyankar S, Al-Kadhimi Z, et al. Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). The Lancet Haematology. 2019;6(3):e132–e43. [PubMed: 30824040]
9. Tisdale JF, Eapen M, Saccardi R. HCT for Nonmalignant Disorders. Biology of Blood and Marrow Transplantation. 2013;19(1, Supplement):S6–S9. [PubMed: 23104188]
10. Bolaños-Meade J, Fuchs EJ, Luznik L, Lanzkron SM, Gamper CJ, Jones RJ, et al. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood. 2012;120(22):4285. [PubMed: 22955919]
11. DeZern AE, Zahurak M, Symons H, Cooke K, Jones RJ, Brodsky RA. Alternative Donor Transplantation with High-Dose Post-Transplantation Cyclophosphamide for Refractory Severe Aplastic Anemia. Biology of Blood and Marrow Transplantation. 2017;23(3):498–504. [PubMed: 28013015]
12. Harris AC, Young R, Devine S, Hogan WJ, Ayuk F, Bunworasate U, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. Biology of Blood and Marrow Transplantation. 2016;22(1):4–10. [PubMed: 26386318]
13. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2005;11(12):945–56.
14. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912–9. [PubMed: 15994282]
15. Bacigalupo A, Hows J, Gordon-Smith EC, Gluckman E, Van Lint MT, Congiu M, et al. Bone marrow transplantation for severe aplastic anemia from donors other than HLA identical siblings: a report of the BMT Working Party. Bone Marrow Transplant. 1988;3(6):531–5. [PubMed: 3063321]

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16. Perez-Albuerne ED, Eapen M, Klein J, Gross TJ, Lipton JM, Baker KS, et al. Outcome of unrelated donor stem cell transplantation for children with severe aplastic anemia. British Journal of Haematology. 2008;141(2):216–23. [PubMed: 18307564]
17. Horan J, Wang T, Haagenson M, Spellman SR, Dehn J, Eapen M, et al. Evaluation of HLA matching in unrelated hematopoietic stem cell transplantation for nonmalignant disorders. Blood. 2012;120(14):2918–24. [PubMed: 22829628]
18. Deeg HJ, O'Donnell M, Tolar J, Agarwal R, Harris RE, Feig SA, et al. Optimization of conditioning for marrow transplantation from unrelated donors for patients with aplastic anemia after failure of immunosuppressive therapy. Blood. 2006;108(5):1485–91. [PubMed: 16684959]
19. Passweg JR, Baldomero H, Bader P, Basak GW, Bonini C, Duarte R, et al. Is the use of unrelated donor transplantation leveling off in Europe? The 2016 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transplant. 2018;53(9):1139–48. [PubMed: 29540849]
20. Bacigalupo A Alternative donor transplants for severe aplastic anemia. ASH Education Program Book. 2018;2018(1):467–73.
21. Xu L-P, Jin S, Wang S-Q, Xia L-H, Bai H, Gao S-J, et al. Upfront haploidentical transplant for acquired severe aplastic anemia: registry-based comparison with matched related transplant. J Hematol Oncol. 2017;10(1):25-. [PubMed: 28107815]
22. Xu LP, Xu ZL, Wang FR, Mo XD, Han TT, Han W, et al. Unmanipulated haploidentical transplantation conditioning with busulfan, cyclophosphamide and anti-thymoglobulin for adult severe aplastic anaemia. Bone Marrow Transplant. 2018;53(2):188–92. [PubMed: 29334367]
23. Gupta V, Eapen M, Brazauskas R, Carreras J, Aljurf M, Gale RP, et al. Impact of age on outcomes after bone marrow transplantation for acquired aplastic anemia using HLA-matched sibling donors. Haematologica. 2010;95(12):2119–25. [PubMed: 20851870]
24. Bacigalupo A How I treat acquired aplastic anemia. Blood. 2017;129(11):1428–36. [PubMed: 28096088]
25. Shin SH, Jeon YW, Yoon JH, Yahng SA, Lee SE, Cho BS, et al. Comparable outcomes between younger (40 years) and older (>40 years) adult patients with severe aplastic anemia after HLA-matched sibling stem cell transplantation using fludarabine-based conditioning. Bone Marrow Transplant. 2016;51(11):1456–63. [PubMed: 27348538]

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Table 1.

Clinical Characteristics and Outcomes

	A	B	C	D	E	F	G	h	I	J	K	L	M	N	O	P	Q
1		**baseline characteristics**						**donor/graft characteristics**			**engraftment (days)**		**GVHD**		**Follow up**		**Infections**
2	**subject number**	**Age**	**Sex**	**Diagnosis**	**Previous Therapy**	**HCT-CI**	***ANC on admission cells/μL**	**Donor relationship**	**degree of HLA match**	**infused CD34+ cells/kg (× 10^6)**	**Neutrophil**	**Platelet**	**aGVHD**	**cGVHD**	**alive**	**follow-up (months)**	**infectious complications prior to day +100**
3	1	39	M	dba	steroids	0	10300	half-brother	haplo	1.54	21	43	none	none	Yes	63	none
4	2	43	M	SAA	ATG/CSA	0	510	brother	haplo	4.86	17	30	S1 skin	none	yes	46	c. diff colitis, BK cystitis
5	3	24	M	SAA	ATG/CSA, promacta	0	3690	sister	haplo	4.05	21	49	none	none	Yes	36	influenza, adenovirus cystitis
6	4	44	F	PNH	steroids, eculizumab	3	2260	sister	full	2.68	16	21	none	moderate eyes	Yes	24	BK cystitis
7	5	42	M	SAA	steroids/ATG/CSA	0	390	cousin	haplo	20.5	18	31	S1 skin	none	Ye	25	bacteremia, BK csystitis
8	6	56	F	SAA	steroids/ATG/CSA	5	2580	unrelated	full	5.65	27	31	none	none	Yes	14	none
9	7	39	M	DBA	steroids, tesosterone	1	6320	cousin	haplo	3.69	21	35	S1 skin	mild eyes	Yes	12	none
10	8	73	M	SAA	ATG/CSA/ promacta	0	3580	unrelated	full	4.77	25	57	none	mild eyes	Yes	8	endocarditis
11	9	46	F	SAA	promacta	0	520	cousin	haplo	5.87	17	23	none	none	Yes	4	none

*ANC on admission for BMT prior to initiating conditioning chemotherapy

ANC- absolute neutrophil count, SAA- severe aplastic anemia, DBA – Diamond Blackfan Anemia, ATG- anti-thymocyte globulin, CSA-cyclosporine, Cy-cyclophosphamide, haplo- haploidentical

Bone Marrow Transplant. Author manuscript; available in PMC 2021 July 14.