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Long-term SLE Disease Control after Allogeneic Bone Marrow Transplantation

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Abstract

Systemic lupus erythematosus (SLE), a disorder of the immune system, is potentially curable by allogeneic bone marrow transplantation (alloBMT). Until recently, alloBMT was limited by donor availability and toxicity. Reduced intensity conditioning (RIC) combined with post-transplantation cyclophosphamide (PTCy) has improved the availability and safety of alloBMT permitting its exploration in severe-refractory autoimmune illnesses. We report the six-year follow-up of a young female whose refractory SLE-associated nephrosis resolved after RIC alloBMT with PTCy.

Keywords

SLE; alloBMT

Allogeneic bone marrow transplantation (alloBMT) by eradicating donor hematopoiesis can extinguish autoreactive lymphocytes. AlloBMT is currently utilized to treat inborn errors of metabolism, bone marrow failure, hemoglobinopathies and hematologic malignancies. Its use in other illness has been limited by preparative regimen toxicity, donor availability, poor engraftment and late transplant toxicities such as graft-versus-host-disease (GVHD). However, reduced intensity conditioning (RIC) in combination with use of alternative donors has expanded the safety and access to alloBMT (1). Importantly, post-transplantation cyclophosphamide (PTCy) (2–4) has reduced the rate of GVHD from related haploidentical donors to that seen with matched donors (5–7). This improved access and safety of alloBMT may permit its use to treat severe-refractory autoimmune illnesses. Here we present the long-term follow-up of a patient with refractory systemic lupus erythematosus (SLE) who six years ago received a RIC alloBMT with PTCy primarily for sickle cell anemia.

In the summer of 2003, an 18 year-old, female of Nigerian descent was diagnosed with systemic lupus based on antinuclear antibodies, anti-Smith antibodies, a low complement component 3 and polyarthritis. Her past medical history was significant for sickle cell anemia. Her initial systemic lupus erythematosus (SLE) treatment was prednisone and high-dose mycophenolate mofetil. Despite this intervention, within six months, she developed

focal proliferative and membranous lupus nephritis with nephrotic range proteinuria. Concurrently, she suffered an anticardiolipin IgG antibody mediated renal vein thrombosis and anticoagulation was initiated. Her renal disease would eventually prove to be refractory to tacrolimus; pulse cyclophosphamide was introduced. After eleven cyclophosphamide infusions (October 2004 through August 2006), rituximab was initiated in September of 2006 as a remittive agent. However, intense rituximab infusion reactions required its discontinuation just after two infusions; she continued to receive an additional three quarterly-infusions of cyclophosphamide (completed June 2007). While, the nephrosis improved on therapy, her steroid dose could not be tapered below 7.5mg daily. Her SLEDAI score before alloBMT was calculated at 6.

Her hemoglobin SS induced vaso-occlusive and bone pain crises. The early years of her disease were mild with 2–3 pain crises per year managed mostly at home. However, since the diagnosis of SLE, her sickle cell disease had become more complicated. In late 2004, her hemoglobin F quantification was 10% (>30% protects the cell from sickling) and Hgb S 83%. During the year prior to alloBMT, she suffered pain crises once every 1–2 months, many of which required hospitalization and red cell transfusion support. Before alloBMT, controlling her sickle cell pain required 120mg of extended-release morphine daily plus breakthrough opiate use.

At 25 years of age, she underwent a RIC, haploidentical, CMV+ allogeneic bone marrow transplant from her brother with sickle cell trait (Hgb: ASA2). Her preparative conditioning regimen was fludarabine (day –6 through day –2), cyclophosphamide (day –6, day –5), antithymocyte globulin (day –4, day –3) and 200cGY total body irradiation (day –1). On day 0 (9/17/10), she underwent a red cell exchange transfusion followed by infusion of her brother's hematopoietic stem cells. For GVHD prophylaxis, she received PTCy (day +3, day +4), mycophenolate mofetil and tacrolimus (both starting day +5). Her baseline 7.5mg of daily prednisone was maintained. Her course was complicated by tacrolimus induced CMV viremia and posterior reversible encephalopathy syndrome (PRES). Both were medically managed without long-term sequel. She attained neutrophil recovery on day +17 and full donor whole blood and T-cell engraftment by day +28. Mycophenolate mofetil and sirolimus (substituted for tacrolimus secondary to PRES) were discontinued on day +35 and day +360, respectively. She never developed acute nor chronic GVHD and remains with full T-cell engraftment.

Nine months after alloBMT, her anticoagulation therapy was stopped and her opiate requirements began to wane. By fourteen months continuous opiate use ended. In the immediate post-transplant period her protein-creatinine ratio increased and plaquinil 200mg twice daily was initiated on day +76. A prednisone tapered was initiated at 21 months and completed 2.5 years after alloBMT. She had normalization of her urine protein 2.7 years after alloBMT. Her medical course was further complicated by bilateral septic necrosis of her humeri requiring bilateral humeral head core decompression (1.6 years and 2.4 years), cryptogenic, marked-pitting lower extremity lymphedema responsive to local measures (2.6 years –ongoing), cholelithiasis requiring a cholecystectomy (3.6 years), grade I/II thrombocytopenia (3.9 years – ongoing), and transient pityriasis rosea (4.3 years). She is currently 5.5 years post alloBMT, she retains full engraftment, her remittive therapy is

limited to plaquinil 200mg twice daily and her current SLEDAI score is 3 secondary to a low complement level and moderate thrombocytopenia. Her urine protein to creatinine ratio normalized at 15 months (Figure 1). At thirty years of age, she has regular monthly menses and wishes to conceive.

The combination of RIC and PTCy has markedly expanded access and lowered the morbidity and mortality of alloBMT. After RIC, engraftment is not synonymous with neutrophil recovery. Accordingly, peripheral blood donor-patient chimerism analysis determines graft status. (8) Additionally, long-term graft survival does not occur when donor cells are lost within the T-cell compartment. (9, 10) In the malignant setting, RIC with PTCy is associated with a >90% T-cell engraftment. However, lower engraftment rates are encountered alloBMT for non-malignant conditions, especially with RIC. (11, 12)

This patient underwent alloBMT for two non-malignant conditions sickle cell anemia and SLE. AlloBMT is an established therapy for hemoglobinopathies. However, alloBMT for autoimmune illnesses is novel. We and others have established a role in high dose chemotherapy with and without stem cell rescue for severe refractory autoimmune illnesses. (13–16) And while, high dose chemotherapy improves quality of life, most patients relapse within 5 years. AlloBMT holds the promise of disease eradication. As compared to patients with hemoglobinopathies, full donor chimerism with RIC may be easier to achieve in refractory SLE patients given their previous immunosuppressive therapies. The morbidity and mortality of RIC with PTCy is low and since PTCy expands the donor pool, the majority of refractory lupus patients would potentially be eligible for such a transplant. The transient CMV viremia experienced by this patient is commonly encountered during alloBMT. Since her alloBMT, both illnesses are well controlled. In terms of her SLE: she has stopped all immunosuppression except plaquinil and her urine to protein creatinine ratio which was once as high as 5.27 has normalized. Given the experience of this index patient, the role of alloBMT in the treatment of refractory autoimmune illnesses deserves exploration.

References

1. Khouri IF, Keating M, Korbling M, Przepiorka D, Anderlini P, O'Brien S, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. *J Clin Oncol*. 1998; 16(8):2817–24. [PubMed: 9704734]
2. Grewal SS, Barker JN, Davies SM, Wagner JE. Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood? *Blood*. 2003; 101(11):4233–44. [PubMed: 12522002]
3. 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(6): 641–50. [PubMed: 18489989]
4. Fuji S, Nakamura F, Hatanaka K, Taniguchi S, Sato M, Mori S, et al. Peripheral blood as a preferable source of stem cells for salvage transplantation in patients with graft failure after cord blood transplantation: a retrospective analysis of the registry data of the Japanese Society for Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2012; 18(9):1407–14. [PubMed: 22430086]
5. McCurdy SR, Kanakry JA, Showel MM, Tsai HL, Bolanos-Meade J, Rosner GL, et al. Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide. *Blood*. 2015; 125(19):3024–31. [PubMed: 25814532]

6. Bashey A, Zhang X, Sizemore CA, Manion K, Brown S, Holland HK, 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):1310–6. [PubMed: 23423745]
7. Raiola AM, Dominietto A, di Grazia C, Lamparelli T, Gualandi F, Ibatìci A, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. *Biol Blood Marrow Transplant.* 2014; 20(10):1573–9. [PubMed: 24910379]
8. Perez-Simon JA, Caballero D, Diez-Campelo M, Lopez-Perez R, Mateos G, Canizo C, et al. Chimerism and minimal residual disease monitoring after reduced intensity conditioning (RIC) allogeneic transplantation. *Leukemia.* 2002; 16(8):1423–31. [PubMed: 12145680]
9. Kwon M, Martinez-Laperche C, Balsalobre P, Serrano D, Anguita J, Gayoso J, et al. Early peripheral blood and T-cell chimerism dynamics after umbilical cord blood transplantation supported with haploidentical cells. *Bone Marrow Transplant.* 2014; 49(2):212–8. [PubMed: 24212562]
10. Mancardi GL, Saccardi R, Filippi M, Gualandi F, Murialdo A, Inglese M, et al. Autologous hematopoietic stem cell transplantation suppresses Gd-enhanced MRI activity in MS. *Neurology.* 2001; 57(1):62–8. [PubMed: 11445629]
11. Bolanos-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):4285–91. [PubMed: 22955919]
12. Shamshad GU, Ahmed S, Bhatti FA, Ali N. Mixed donor chimerism in non-malignant haematological diseases after allogeneic bone marrow transplantation. *J Coll Physicians Surg Pak.* 2012; 22(12):765–8. [PubMed: 23217481]
13. 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 (Baltimore).* 2011; 90(2):89–98. [PubMed: 21358440]
14. Gladstone DE, Peyster R, Baron E, Friedman-Urevich S, Sibony P, Melville P, et al. High-dose cyclophosphamide for moderate to severe refractory multiple sclerosis: 2-year follow-up (investigational new drug No. 65863). *Am J Ther.* 2011; 18(1):23–30. [PubMed: 19770795]
15. Gladstone DE, Zamkoff KW, Krupp L, Peyster R, Sibony P, Christodoulou C, et al. High-dose cyclophosphamide for moderate to severe refractory multiple sclerosis. *Arch Neurol.* 2006; 63(10):1388–93. [PubMed: 16908728]
16. Petri M, Brodsky RA, Jones RJ, Gladstone D, Fillius M, Magder LS. High-dose cyclophosphamide versus monthly intravenous cyclophosphamide for systemic lupus erythematosus: a prospective randomized trial. *Arthritis Rheum.* 2010; 62(5):1487–93. [PubMed: 20131296]

Figure 1.