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Case report

Allogeneic stem cell transplantation for Evans syndrome

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Summary:

Evans syndrome is a rare disorder characterized by combined autoimmune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA). Standard treatments consist of transfusions, corticosteroids, splenectomy, IVIG, anabolic steroids, vincristine, alkylating agents, or cyclosporine. In a patient with refractory disease, an allogeneic hematopoietic stem cell transplant (HSCT) resulted in complete clinical and serologic remission for more than 30 months. Allogeneic HSCT may be the only current curative therapy for Evans syndrome but may also be complicated by significant toxicities. *Bone Marrow Transplantation* (2001) **28,** 903–905.
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In December 1998, a 28-year-old male patient with refractory Evans syndrome (Hb of 9.1g/dl and platelets of 27×10^9/l) was referred to Northwestern University for an allogeneic matched sibling HSCT. Symptoms first occurred in February 1996 when epistaxis and ecchymosis developed following flu-like symptoms of headache and diarrhea. Thrombocytopenia and anemia were present with platelets of 2×10^9/l, hemoglobin of 8.8 g/dl, and WBC of 6.3×10^9/l. Evidence of hemolysis included hyperbilirubinemia (3.8 mg/dl), an increased LDH (424 U/l), decreased haptoglobin (7 mg/dl), reticulocytosis (corrected reticulocyte count 5.5%), bone marrow erythroid hyperplasia, and a direct Coombs test (DAT) positive for warm reactive anti-IgG and anti-C3D. Evidence for ITP included anti-platelet antibodies and increased megakaryocytes within the marrow. Cytomegalovirus (CMV) antibody was positive for IgM but negative for IgG indicating recent infection. There was no other evidence of coincidental or precipitating infections. Serology was negative for HIV, hepatitis A, B, and C, and indicated past Epstein–Barr virus infection. Anti-nuclear and anti-double stranded DNA antibodies were negative.

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An initial response was obtained with intravenous immunoglobulin (IVIG) and corticosteroids. Due to inability to wean high-dose corticosteroid therapy, or transfusion-dependent cytopenias, the patient was treated and subsequently failed multiple interventions including splenectomy (August 1996), IVIG, danazol, and vincristine (April 1997), azathioprine 100 mg/day (August 1997), IVIG (March 1998), and cyclosporine, IVIG, and vincristine (April 1998). Upon referral for transplant, the patient was platelet and red blood cell (RBC) transfusion-dependent despite prednisone, cyclosporine, and IVIG.

Pre-transplant, the disease and treatment-related complications included hemoglobinuria, malaise, steroid-induced diabetes, vincristine-induced peripheral neuropathy, cyclosporine-induced tremor and nephropathy necessitating daily intravenous hydration, anemia-related syncope, retinal hemorrhage, and respiratory and renal failure that necessitated ICU transfer and respiratory support. Pre-transplant opportunistic infectious included cryptococcal fungemia, persistent CMV viremia, and mycobacterium avium positive blood cultures. Maintenance antimicrobial therapy included liposomal amphotericin B and flucytocine for persistent cryptococcal fungemia, ganciclovir for recurrent CMV viremia, and azithromycin for mycobacterium avium prophylaxis.

The patient was transplanted under IRB and FDA approved protocol IDE 6991. The transplant-conditioning regimen was cyclophosphamide (200 mg/kg) and antithymocyte globulin (90 mg/kg). The allograft was unmanipulated bone marrow enriched with peripheral blood $CD34^+$ cells from the patient's HLA matched sister. $CD34^+$ cell purification was performed utilizing Isolex (Nexell, Irvine, CA, USA) positive selection system. A total of 5.65×10^6 $CD34^+$ cells/kg were infused. Cyclosporine and corticosteroids were continued as GVHD prophylaxis, while liposomal amphotericin B (three times/week), aerosolized pentamidine, and azithromycin were continued as infection prophylaxis. WBC and platelet engraftment occurred on days 10 and 14, respectively. The initial post-transplantation course was uncomplicated. RBC and platelet antibodies gradually disappeared over 3 months. Chimerism studies demonstrated 100% donor engraftment.

Thrombotic thrombocytopenic purpura (TTP) developed 5 weeks after HSCT and resolved with plasmapheresis and discontinuation of cyclosporine. GVHD prophylaxis was changed to FK506 and low-dose corticosteroids. TTP recurred and resolved upon discontinuation of FK506. With

Table 1 High-dose immune suppression with or without hematopoietic stem cell transplantation for ITP, AIHA, or Evans syndrome

Disease	*Author (Ref.)*	*Age/Sex*	*Allied disease*	*Conditioning regimen*	*Graft*	*Outcome*	*Response*
Evans ITP AIHA	Brodsky[9]	31 M 47 F 36 F	None	Cy	None	Alive Died 8 months Died 16 months	PR PR – relapse ITP CR – new ITP
Evans	Martino[10]	23/F	None	NA	NA	Died of ICB after mobilization	NA – died
Evans	Musso[11]	19/F	SLE	Cy/ATG	Auto	Alive	CR 8 months – DAT positive
ITP	Skoda[12]	39	None	Cy	Auto-TCD	Alive	NR
ITP	Marmont[13]	44/M	None	TT/Cy	Auto-TCD	Alive	NR
ITP	Lim[14]	43/F 19/M	None	Cy	Auto	One died after 2nd autograft	CR but relapsed at 12 months CR but relapsed at 18 months
ITP	Demirer[15]	46/M	SCLC	TT/Mel/CBDCA	Auto	Alive	CR after 6 months
ITP	Huhn[16]	N/A	None	Cy	Auto-TCD	Alive	PR in 2, NR in 2
AIHA	Pillard[17]	8/M	None	1st HSCT Cy/ATG 2nd HSCT BEAM/ATG/CsA	Auto-TCD Auto-TCD	NA Alive	NR CR after 20 months
AIHA	Jindra[18]	48/M	CLL	BEAM	Auto-TCD	Alive	CR after 23 months
Evans	Raetz[19]	4/M	None	Cy/TBI	Allo-cord blood	Died liver failure day 289	CR
AIHA	De Stefano[20]	12/M	Thalassemia	1st transplant: TAI/Cy/Campath-1G	Auto-TCD	NA	NR
				2nd transplant: Bu/TT/Flu	MUD-BM	Alive	CR after 18 month
PRCA	Muller[21]	16 F	None	Cy/ATG	Allo-BM	Alive	Mixed chimerism at 6 months, 100% autologous recovery at 1 year. Disease still in CR

AIHA = autoimmune hemolytic anemia; ATG = antithymocyte globulin; BEAM = BCNU/VP-16/cytarabine/melphalan; BM = bone marrow; Bu = busulfan; CBDCA = carboplatin; CLL = chronic lymphocytic leukemia; CR = complete response; Cy = cyclophosphamide; CsA = cyclosporine; Flu = fludarabine; ICB = intracranial bleeding; ITP = immune thrombocytopenia purpura; HSCT = hematopoietic stem cell transplant; Mel = melphalan; MUD = matched unrelated donor; NA = not applicable; NR = no reponse; PR = partial response; PRCA = pure red cell aplasia; SCLS = small cell lung cancer; TAI = thoraco-abdominal irradiation; TCD = T cell depletion of graft; TT = thiotepa.

no evidence of GVHD, TTP, immune-mediated cytopenias, or infection, the patient was discharged home on mycophenolate mofetil and prednisone. Since the patient was unable to tolerate cyclosporine or FK505 due to TTP, while on only corticosteroid immune suppression, acute gastrointestinal grade IV GVHD occurred. Treatment consisted of high-dose corticosteroid, oral beclomethasone, mycophenolate mofetil, and daclizumab.

Extensive chronic cutaneous and gastrointestinal GVHD developed. Post-transplant opportunistic infections have included Pseudomonas and Nocardia bacteremia, CMV retinitis, and persistent CMV reactivation. Platelet counts have been intermittently suppressed by medications and infections but recover to normal. Platelet antibodies and direct and indirect Coombs test remain negative without evidence of hemolysis. Currently, the skin has improved to normal and there are no GI symptoms on mycophenolate mofetil, prednisone, and infliximab. The last platelet transfusion was in August 2000 and RBC transfusion was 4 months ago. Platelet count is currently $>200 \times 10^9$/dl and hemoglobin is 12.0 g/dl.

Discussion

This patient's clinical course demonstrates refractory autoimmune-mediated hemolysis and thrombocytopenia with pre-transplant life-threatening complications. In severe Evans syndrome, treatment options are limited and the disease can be fatal.[1] Although the literature is limited, Evans syndrome appears to be a more aggressive and fatal disease than either ITP or AIHA alone.[2,3] Treatment for Evans syndrome is often ineffective. Survival data are available on only small numbers of patients over a short period of time: four of 12 patients followed for 8 years died;[4] three of 42 patients followed for 3 years died;[5] three of 10 patients followed for 13 years died;[6] and, in another report, four of 11 patients followed for 8 years died.[1] The cause of death is generally bleeding, especially intracranial hemorrhage, pulmonary emboli, or infection.

Evans syndrome may be primary without an underlying disorder or associated with lymphoproliferative disorders (eg CLL), autoimmune disease (eg SLE), or medications.[7] Immune abnormalities, intrinsic to the disease and/or to

chronic immune suppression, are associated with Evans syndrome.[8] This patient's course demonstrated numerous opportunistic infections mandating pre-, peri- and post-transplant anti-microbial therapy.

High-dose immune suppression without autologous stem cell support has been used to treat Evans syndrome, ITP and AIHA (Table 1). Of three patients treated with high-dose cyclophosphamide (200 mg/kg) without stem cell support, only partial responses occurred and two died of relapsed disease and of new onset of ITP.[9] In the published literature, 13 patients have received high-dose cyclophosphamide and autologous HSCT. One died during mobilization; four patients had no response; two had a partial response; two had a complete response but clinically relapsed; one had a complete clinical remission but remains DAT (direct antiglobulin test) positive; and three remain in complete remission with short follow-up of 6, 20, and 23 months.[10–18] These data suggest that the possibility of a durable remission or cure from high-dose immune suppression with or without autologous HSCT for ITP, AIHA, or Evans syndrome is unlikely for the majority of patients.

To our knowledge, this is the first adult case of primary Evans syndrome cured by allogeneic hematopoietic transplantation. Allogeneic HSCT using sibling matched umbilical cord blood,[19] matched unrelated BM[20] or matched sibling BM[21] has been used to treat Evans syndrome, AIHA or pure red cell aplasia (PRCA), respectively. In none of the three cases did the disease relapse after allogeneic HSCT although follow-up was short: 289 days, 18 months and 3 years, respectively. In our patient, there has been no evidence of immune mediated thrombocytopenia or hemolysis for 2 years and 6 months since the allogeneic transplant. The patient is 100% donor chimeric and antibodies to RBCs and platelets are negative. However, the post-transplant course has been complicated by drug-related TTP, chronic extensive GVHD, and immune suppression-related opportunistic infections.

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