Y. Oyama, MD
R. Sufit, MD
Y. Loh, MD
L. Statkute, MD
K. Yaung, RN
K. Quigley, RN
E. Gonda, RN
D. Spahovic, MD
D. Bronesky, MD
R.K. Burt, MD

NONMYELOABLATIVE AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR REFRACTORY CIDP

Most patients with chronic inflammatory demyelinating polyneuropathy (CIDP) initially respond to corticosteroids, immunosuppressive drugs, IV immune globulin (IVIg), and plasma exchange (PE). However, more than half relapse, with some developing a recurrent or persistent clinical course resulting in severe disability and even death.[1,2] Nonmyeloablative autologous hematopoietic stem cell transplantation (HSCT) for severe autoimmune diseases has demonstrated promising results, with reports of durable remissions and lower toxicity compared to myeloablative HSCT.[3] Herein, we report the first patient treated in a phase I trial of autologous HSCT utilizing a nonmyeloablative regimen for refractory CIDP.

Methods. Eligibility criteria include age 65 years or less; definite or probable CIDP according to the criteria of the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force; failure of standard therapy, i.e., incomplete response or relapse after corticosteroids, IVIg, or PE; and failure to respond to at least one second-line immunosuppressive drug (methotrexate, azathioprine, cyclosporine, tacrolimus, or mycophenolate mofetil [MMF]). CD34-enriched peripheral blood stem cells (PBSC) are harvested after administration of cyclophosphamide 2 g/m^2 and granulocyte colony-stimulating factor (G-CSF). Following a conditioning regimen consisting of cyclophosphamide (200 mg/kg divided over 4 days) and rabbit antithymocyte globulin (ATG) (5.5 mg/kg divided over 5 days), PBSC are infused 48 hours after completion of cyclophosphamide. IVIg, PE, and all immunosuppressive drugs are discontinued upon PBSC procurement, except systemic corticosteroids that are tapered gradually.

Results. The patient was a 32-year-old woman who presented with gradual onset of paresthesia and twitching of the face and limbs, and progressive weakness of both upper extremities, evolving over several weeks to include her lower extremities as well. She was areflexic with weakness more marked proximally and in the upper extremities. Based on nerve conduction studies consistent with a demyelinating polyneuropathy, she was treated with IVIg weekly for 5 weeks with clinical improvement. However, when this was reduced in frequency, weakness recurred and she was commenced on daily/alternate-day PE, to which she responded. Attempts to taper PE resulted in worsened neurologic symptoms which progressed despite addition of prednisone (80 mg/day). A 3-month trial of methotrexate was complicated by anemia. She was maintained on twice-weekly PE but this was complicated by three episodes of pheresis catheter-related bacteremia and resultant disease exacerbations. MMF was then added with unsatisfactory result. During periods of exacerbation, she was unable to raise her arms against gravity or handle objects steadily, and could not ambulate more than 30 meters or climb stairs. Despite maintenance PE, the patient continued to have recurrent exacerbations and line infections resulting in referral for HSCT 30 months after disease onset.

HSCT was generally well-tolerated with no unexpected non-hematologic toxicities. Neutrophil counts recovered by day 11; platelet counts by day 9 after HSCT. She was successfully weaned off PE and all immunosuppressants, apart from MMF which was discontinued after 6 months. She has had no disease exacerbations since HSCT, with a follow-up of 22 months. Clinical improvement has been gradual but definite, and by 6 months post-transplant, her upper extremity strength had improved and she could ambulate and climb stairs. Rankin functional score improved from 4 to 1. Nerve conduction studies before and 1 year post-transplant are shown in the table.

Discussion. A previous report of autologous HSCT for CIDP used a myeloablative conditioning regimen consisting of multiple chemotherapeutic agents, with neutrophil recovery reported at 16 days. The patient responded but toxicity was not discussed.[4] High-dose cyclophosphamide without stem cell infusion has been reported to have encouraging results.[5] By utilizing high-dose cyclophosphamide along with ATG, we are able to achieve potent immunosuppression without ablating the entire marrow compartment, thus avoiding potentially lethal regimen-related toxicities.[3,6] PBSC were infused in order to shorten the duration of neutropenia, as we have shown the speed of neutrophil recovery correlates with dose of infused PBSC.[7]

While CIDP may be controlled in the majority of patients, a subset with high immunosuppressant requirements and chronic dependence on PE are at risk of severe disability, and even death,

Table Nerve conduction studies

	Pretransplant	1 year post-transplant
Motor		
Right median		
Latency (ms) elbow–APB	12.2	10.2
Wrist–APB	5.3	4.2
CV (m/s)	36	41
Amplitude (MV) elbow–APB	5.6	10.4
Wrist–APB	5.5	12.4
Right ulnar		
Latency (ms) elbow–ADM	11.7	8.7
Wrist–ADM	4.1	4.1
CV (m/s)	36	51
Amplitude (MV) elbow–ADM	9.8	7.9
Wrist–ADM	10.0	7.7
Right peroneal		
Latency (ms) knee–EDB	14.1	10.9
Ankle–EDB	5.2	4.1
CV (m/s)	40	46
Amplitude (MV) knee–EDB	6.0	5.9
Ankle–EDB	7.3	6.8
Right posterior tibial		
Latency (ms) ankle–AH	6.8	5.2
Amplitude (mv) ankle–AH	12.6	13.1
Sensory		
Right median		
Peak latency (ms) wrist–2nd	4.0	3.7
Amplitude (mv) wrist–2nd	32	18
Right ulnar		
Peak latency (ms) wrist–5th	3.7	3.6
Amplitude (mv) wrist–5th	28	23
Right sural		
Peak latency (ms) calf–ankle	3.9	3.8
Amplitude (mv)calf–ankle	20	16

APB = abductor pollicis brevis; CV = conduction velocity; MV = millivolt; ADM = abductor digiti minimi; EDB = extensor digitorum brevis; AH = abductor hallucis; mv = microvolt; 2nd = index finger; 5th = 5th finger.

both from the disease itself and the complications of therapy.[1,2] The risks of long-term immunosuppressants, high-dose steroid therapy with its attendant risks of both infections and metabolic derangements, and complications of indwelling vascular devices warrant exploring alternative options. This report illustrates that HSCT can be performed safely and may justify earlier consideration in selected patients with refractory disease. Before HSCT, our patient reported accumulation of weakness between plasmapheresis sessions every 10 days rendering "even simple stairs and opening jars difficult." HSCT markedly ameliorated disease manifestations and permitted discontinuation of corticosteroids, IVIg, and PE, all attempts to which were unsuccessful prior to HSCT. Although follow-up is short (22 months), this promising result forms the basis of further studies of autologous HSCT for refractory CIDP.

From the Department of Medicine Division of Immunotherapy (Y.O., Y.L., L.S., K.Y., K.Q., E.G., D.S., D.B., R.K.B.) and Department of Neurology (R.S.), Feinberg School of Medicine, Northwestern University, Chicago, IL.

Disclosure: The authors report no conflicts of interest. Received July 16, 2006. Accepted in final form April 19, 2007.

Address correspondence and reprint requests to Dr. Richard Burt, Division of Immunotherapy, Feinberg School of Medicine, Northwestern University, 750 N. Lakeshore Dr. 649, Chicago, IL 60611; rburt@northwestern.edu

1. Gorson KC, Allan G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. Neurology 1997;48:321–328.
2. McCombe PA, Pollard JD, McLeod JG. Chronic inflammatory demyelinating polyradiculoneuropathy. A clinical and electrophysiological study of 92 cases. Brain 1987;110:1617–1630.
3. Burt RK, Marmont A, Oyama Y, et al. Randomized controlled trials of autologous hematopoietic stem cell transplantation for autoimmune diseases: the evolution from myeloablative to lymphoablative transplant regimens. Arthritis Rheum 2006;54:3750–3760.
4. Vermeulen M, Van Oers MH. Successful autologous stem cell transplantation in a patient with chronic inflammatory demyelinating polyneuropathy. J Neurol Neurosurg Psychiatry 2002;72:127–128.
5. Brannagan TH III, Pradhan A, Heiman-Patterson T, et al. High-dose cyclophosphamide without stem-cell rescue for refractory CIDP. Neurology 2002;58:1856–1858.
6. Gratwohl A, Passweg J, Bocelli-Tyndall C, et al. Autologous hematopoietic stem cell transplantation for autoimmune diseases. Bone Marrow Transplant 2005;35:869–879.
7. Statkute L, Verda L, Oyama Y, et al. Mobilization, harvesting and selection of peripheral blood stem cells in patients with autoimmune diseases undergoing autologous hematopoietic stem cell transplantation. Bone Marrow Transplant 2007;39:317–329.