

High-Dose Cyclophosphamide Without Stem Cell Transplantation in Systemic Lupus Erythematosus

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Objective. High-dose chemotherapy followed by hematopoietic stem cell transplantation is increasingly being studied as a treatment for severe autoimmune disorders, such as systemic lupus erythematosus (SLE). High-dose cyclophosphamide, the foundation of virtually all conditioning regimens for stem cell transplantation, is not myeloablative; therefore, when high-dose cyclophosphamide is used alone, autografting, with its potential for reinfusing autoreactive effector cells, is not required. We undertook this study to investigate the safety and efficacy of high-dose cyclophosphamide without stem cell transplantation in refractory SLE.

Methods. We treated 14 patients with moderate-to-severe SLE that had been refractory to corticosteroids and one or more additional immunosuppressive drugs. All patients received 50 mg/kg of cyclophosphamide for 4 consecutive days followed by 5 μ g/kg granulocyte colony-stimulating factor until the neutrophil count was 1×10^9 /liter for 2 consecutive days. Patients were followed up monthly for disease activity using the physician's global assessment, SLE Disease Activity Index, and assessment of functioning of involved organs. The Responder Index for Lupus Erythematosus was used to define partial or complete response.

Results. The median time to achieve a neutrophil count of 0.5×10^9 /liter was 14 days (range 11–22 days) after the last dose of cyclophosphamide. Patients re-

quired a median of 2 units (range 2–5) of packed red blood cells, and a median of 16 days (range 0–23 days) elapsed from the last dose of cyclophosphamide to the last platelet transfusion. There were no deaths or fungal infections. Significant improvements in physician's global assessment (mean difference 1.4; $P < 0.0001$), SLE Disease Activity Index (mean difference 4.1; $P = 0.0039$), and prednisone dosage (mean difference 14.9 mg/day; $P = 0.002$) were observed. Responses, including 5 durable complete responses, were observed in all organ systems (renal, central nervous system, and skin) with involvement that had led to patient enrollment.

Conclusion. High-dose cyclophosphamide without stem cell transplantation leads to rapid hematopoietic reconstitution and has significant clinical benefit in patients with refractory SLE. Therefore, this approach deserves further study.

Despite improved survival rates in patients with systemic lupus erythematosus (SLE) and other autoimmune disorders, there remains a subset of patients in whom the disease is refractory to therapy or who require toxic dosages of immunosuppressive drugs. Standard therapy for severe renal or central nervous system (CNS) SLE is monthly intravenous (IV) bolus cyclophosphamide in doses of 500–1,000 mg/m² body surface area. The superior efficacy of this therapy compared with corticosteroids alone has been proven for diffuse proliferative glomerulonephritis (1,2) and has been suggested in case series of SLE with CNS involvement (3). Monthly IV bolus cyclophosphamide has a safety profile superior to that of daily oral cyclophosphamide, but important toxicities include infections, premature ovarian failure in two-thirds of women over age 31 (4), and a possible increase in gynecologic malignancies (5).

There is now great optimism that high-dose cyclophosphamide therapy followed by hematopoietic stem cell transplantation might induce treatment-free remissions in a variety of severe autoimmune diseases (6–9).

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Interest in this approach emanates from several animal models demonstrating marked reversal or eradication of autoimmunity following syngeneic bone marrow transplantation (10,11). Furthermore, there are reports of allogeneic bone marrow transplantation (performed chiefly for life-threatening hematologic diseases) in which a concurrent autoimmune disease was eradicated (12,13). Thus, interest is increasing in the use of autologous hematopoietic stem cell transplantation following immunoablative conditioning regimens. A potential concern with this approach is that autoreactive effector cells infused with the autograft may reestablish autoimmunity (7,14).

In an effort to circumvent the problem of reinfusing autoaggressive effector cells without assuming the risk of allografting (i.e., graft-versus-host disease), we have utilized high-dose cyclophosphamide (200 mg/kg) without stem cell transplantation for the treatment of severe autoimmune disorders. High-dose immunoablative cyclophosphamide alone has led to long-term remissions in aplastic anemia (15,16) and other autoimmune disorders (17). The unique pharmacology of high-dose cyclophosphamide is responsible for its ability to induce maximal immunosuppression without myeloablation. Hematopoietic stem cells express high levels of aldehyde dehydrogenase, an enzyme responsible for cellular resistance to cyclophosphamide (18–20). Conversely, immunologic effector cells, such as B lymphocytes, T lymphocytes, and natural killer cells, express low levels of aldehyde dehydrogenase and are extremely sensitive to the cytotoxic properties of cyclophosphamide (18). Potential advantages of this approach, which include eliminating the risk of reinfusing autoreactive effector cells and reduced cost, are unproven and would require a randomized trial comparing stem cell transplantation with high-dose cyclophosphamide alone. We now report the results of a study of high-dose cyclophosphamide without stem cell support in 14 patients with refractory SLE.

PATIENTS AND METHODS

Patient eligibility and exclusion criteria. SLE patients were eligible if they met at least 4 of the American College of Rheumatology (ACR) classification criteria (21) and if they had moderate-to-severe SLE that had been resistant to previous courses of corticosteroids and one or more immunosuppressive drugs. All patients gave informed consent for study participation, and the study was approved by the Institutional Review Board of Johns Hopkins University. Exclusion criteria included age >70 years, a serum creatinine concentration

>3.0 mg/dl, a cardiac ejection fraction of <45%, or any underlying malignancy.

SLE assessment. Patients were followed up monthly for assessment of disease activity (physician's global assessment on a 0–3 visual analog scale and SLE Disease Activity Index [22]) (23). A complete responder was defined as having no disease activity and receiving physiologic or lower doses of prednisone and no other immunosuppressive drugs. Complete and partial responders were both defined using the Responder Index for Lupus Erythematosus (RIFLE) (24). For renal lupus, a partial response required a reduction of at least 50% in the 24-hour total protein excretion.

High-dose immunoablative cyclophosphamide. Cyclophosphamide (50 mg/kg) was administered for 1 hour through a Hickman catheter on days 1–4. Six days after the last dose of cyclophosphamide, all patients received granulocyte colony-stimulating factor (5 μ g/kg/day) until the neutrophil count was 1×10^9 /liter for 2 consecutive days. The dose of cyclophosphamide was based on the ideal body weight as determined by the Metropolitan Life table (25,26). If the patient's actual weight was less than the ideal body weight, the actual body weight was used to calculate the cyclophosphamide dose. IV mesna (10 mg/kg) 30 minutes before cyclophosphamide and then 3, 6, and 8 hours after cyclophosphamide was administered in all patients as prophylaxis for hemorrhagic cystitis.

Supportive care. IV ondansetron (32 mg) was administered to all patients 1 hour before each dose of cyclophosphamide. All patients received prophylactic antibiotic support, consisting of fluconazole (400 mg/day), norfloxacin (400 mg/day), and valacyclovir (500 mg twice a day, if antibodies to herpes simplex were present), beginning the day after the last dose of cyclophosphamide and continuing until the neutrophil count exceeded 0.5×10^9 /liter. Dapsone (100 mg 3 times a week for 6 months) was administered for *Pneumocystis carinii* prophylaxis. Packed red blood cell transfusions were administered to maintain a hematocrit level >25%. Platelet transfusions were administered for bleeding and/or to maintain a platelet count $>10 \times 10^9$ /liter.

Statistical analysis. All variables were prospectively entered into a spreadsheet database. Results were expressed as the mean \pm SD. Means were compared using Student's *t*-test (JMP Statistical Software Package, Macintosh Operating System; SAS Institute, Cary, NC). *P* values less than or equal to 0.05 were considered statistically significant.

RESULTS

Patients. Fourteen SLE patients were entered in this trial (Table 1). All patients met at least 4 of the revised ACR classification criteria for SLE (21). Twelve patients (86%) were female and 4 were African American; patients' mean \pm SD age was 35 ± 10 years. Nine patients entered the trial because of renal lupus, 5 with diffuse proliferative glomerulonephritis and 4 with membranous glomerulonephritis. All had ongoing or progressive renal activity despite receiving corticosteroids. In addition, cyclophosphamide had failed in 5 patients (oral cyclophosphamide in 1, monthly pulse IV

Table 1. Patient characteristics and response to high-dose cyclophosphamide*

Patient/ age/sex	Diagnosis or organ involvement	Prior therapies	Therapy for SLE at time of cyclophosphamide screening		Followup from treatment, months	Current status	Current therapy
			Prednisone 60 mg/day, azathioprine 150 mg/day, IV methylprednisolone	Prednisone 10 mg/day, azathioprine 150 mg/day			
1/33/F	CNS, hematologic	Prednisone 60 mg/day, azathioprine 150 mg/day, IV methylprednisolone	Prednisone 10 mg/day, azathioprine 150 mg/day	47	CNS involvement: complete response; hematologic involvement: complete response; new renal involvement†	Mycophenolate 1,500 mg/day†	
2/26/F	Renal	Prednisone 100 mg/day, azathioprine 200 mg/day, hydroxychloroquine 400 mg/day, IV methylprednisolone, IV cyclophosphamide (×1), dapsone 50 mg/day	Prednisone 5 mg/day, azathioprine 200 mg/day, hydroxychloroquine 400 mg/day	43	Complete response	None	
3/45/F	Renal	Prednisone 60 mg/day, IV methylprednisolone, oral cyclophosphamide 150 mg/day	Prednisone 30 mg/day, oral cyclophosphamide 150 mg/day	34	Complete response	None	
4/58/F	CNS, pulmonary hypertension	Prednisone 60 mg/day, azathioprine 200 mg/day, hydroxychloroquine 400 mg/day, IV methylprednisolone, mycophenolate 1,500 mg/day, IV cyclophosphamide (×5)	Prednisone 17.5 mg/day, azathioprine 200 mg/day, hydroxychloroquine 400 mg/day, IV methylprednisolone, mycophenolate 400 mg/day	33	Partial response	Prednisone 10 mg/day, hydroxychloroquine 400 mg/day	
5/36/F	CNS	Prednisone 50 mg/day, azathioprine 200 mg/day, hydroxychloroquine 400 mg/day, IV methylprednisolone, mycophenolate 2,000 mg/day	Prednisone 10 mg/day, azathioprine 200 mg/day, hydroxychloroquine 400 mg/day	32	Complete response	Prednisone 5 mg/day	
6/21/F	Renal	Prednisone 40 mg/day, azathioprine 200 mg/day	Prednisone 40 mg/day, azathioprine 200 mg/day	32	Complete response	None	
7/35/F	Skin	Prednisone 120 mg/day, azathioprine 150 mg/day, hydroxychloroquine 400 mg/day, IV methylprednisolone, mycophenolate 3,000 mg/day, oral cyclophosphamide 200 mg/day, methotrexate 5 mg/week, cyclosporine 300 mg/day, auranofin, dapsone 100 mg/day	Prednisone 20 mg/day, mycophenolate 3,000 mg/day, cyclosporine 300 mg/day	28	Partial response	Prednisone 10 mg/day, cyclosporine 200 mg/day	
8/35/M	Renal	Prednisone 80 mg/day, azathioprine 150 mg/day, hydroxychloroquine 400 mg/day, mycophenolate 2,500 mg/day	Prednisone 5 mg/day, hydroxychloroquine 400 mg/day, mycophenolate 2,000 mg/day	27	No response	Prednisone 5 mg/day, azathioprine 200 mg/day, hydroxychloroquine 400 mg/day	
9/29/F	Renal	Prednisone 180 mg/day, azathioprine 100 mg/day, hydroxychloroquine 400 mg/day, IV methylprednisolone, mycophenolate 2,000 mg/day, cyclosporine 50 mg/day, IV cyclophosphamide	Prednisone 60 mg/day, IV cyclophosphamide, methylprednisolone	27	No response‡	Prednisone 5 mg/day, cyclosporine 200 mg/day	

Table 1. (Cont'd)

Patient/ age/sex	Diagnosis or organ involvement	Prior therapies	Therapy for SLE at time of cyclophosphamide screening	Followup from treatment, months	Current status	Current therapy
10/29/F	Renal	Prednisone 60 mg/day, azathioprine 200 mg/day, IV methylprednisolone, mycophenolate 3,000 mg/day	Prednisone 5 mg/day, mycophenolate 3,000 mg/day	27	Partial response	Prednisone 5 mg/day, mycophenolate 1,500 mg/day
11/24/F	Skin	Prednisone 60 mg/day, azathioprine 50 mg/day, hydroxychloroquine 400 mg/day, IV methylprednisolone, mycophenolate 2,000 mg/day, methotrexate 15 mg/day, dapson 125 mg/day, IM triamcinolone 100 mg/day	Prednisone 40 mg/day, mycophenolate 1,500 mg/day, IM triamcinolone 100 mg/day	25	Partial response	Prednisone 7 mg/day, methotrexate 12.5 mg/week
12/43/M	Renal	Prednisone 40 mg/day, azathioprine 200 mg/day, hydroxychloroquine 400 mg/day, methylprednisolone 48 mg/day, IV methylprednisolone, IV cyclophosphamide ($\times 6$), IV immunoglobulin G	Prednisone 7.5 mg/day, IV cyclophosphamide	23	Partial response	Prednisone 5 mg/day, hydroxychloroquine 400 mg/day, mycophenolate 500 mg/day
13/40/F	Renal	Prednisone 40 mg/day, hydroxychloroquine 400 mg/day, mycophenolate 3,000 mg/day	Prednisone 20 mg/day, mycophenolate 3,000 mg/day	17	Complete response	Prednisone 5 mg/day, hydroxychloroquine 400 mg/day
14/35/F	Renal	Prednisone 60 mg/day, azathioprine 150 mg/day, hydroxychloroquine 400 mg/day, mycophenolate 3,000 mg/day, methotrexate 15 mg/day, IV cyclophosphamide ($\times 4$)	Prednisone 9 mg/day, hydroxychloroquine 400 mg/day, mycophenolate 3,000 mg/day	10	Partial response	Hydroxychloroquine 400 mg/day

* SLE = systemic lupus erythematosus; CNS = central nervous system; IV = intravenous; IM = intramuscular.

† Patient developed new membranous nephropathy.

‡ Patient developed renal failure as she started IV cyclophosphamide and eventually underwent renal transplant.

Table 2. Baseline and last followup data for patients with renal lupus*

Patient	BP, mm Hg		Serum creatinine concentration, mg/dl		Urine protein concentration by dipstick, 0–4+		Urine RBCs, per high-power field		24-hour urine protein excretion, gm/day	
	Baseline	Last followup	Baseline	Last followup	Baseline	Last followup	Baseline	Last followup	Baseline	Last followup
2	110/74	108/70	0.4	0.5	4	0.5	2.5	2.5	1.290	0.112
3	130/100	126/72	1.2	1.5	4	1	1.5	7.5	3.053	0.171
6	112/72	92/60	0.5	0.9	3	1	42	0	2.688	0.196
8	130/82	120/78	0.8	0.9	3	4	2.5	1	6.765	4.760
9	170/118	130/90	2	0.5	4	0	30	1.5	5.200	ND
10	120/80	120/80	0.5	0.4	4	2	0	7.5	2.979	0.750
12	140/80	142/78	1.8	2.7	4	2	30	12.5	12.359	2.551
13	115/64	110/74	0.8	0.9	0.5	2	4	1.5	2.472	0.671
14	106/70	106/70	0.7	0.7	4	0.5	0.5	1	5.005	0.820

* BP = blood pressure; RBCs = red blood cells; ND = not determined (patient underwent renal transplant).

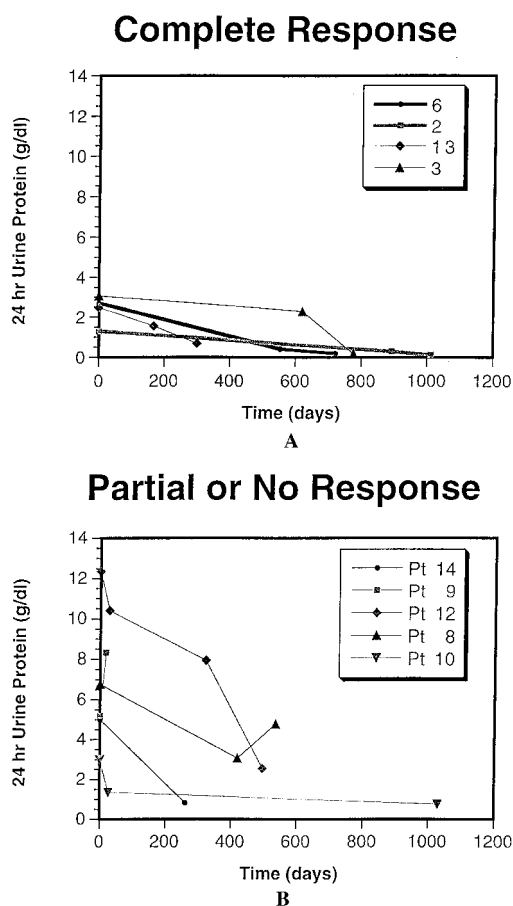


Figure 1. Kidney function before high-dose cyclophosphamide and during followup. **A**, Patients who showed a complete response to high-dose cyclophosphamide (patients 2, 3, 6, and 13). **B**, Patients who showed a partial response or no response to high-dose cyclophosphamide (patients 8–10, 12, and 14). Patient 9 developed renal failure while receiving high-dose cyclophosphamide and eventually underwent renal transplant.

cyclophosphamide in the other 4), mycophenolate mofetil (2,000–3,000 mg/day) had failed in 5, and azathioprine had failed in 7. Three patients were enrolled in the study for CNS SLE, 2 with encephalopathy and 1 with cerebellar ataxia. Two patients were enrolled because of severe refractory cutaneous lupus, 1 with 60% of her body surface area involved with an ulcerating cutaneous lupus rash and 1 with severe pyoderma gangrenosum leading to foot drop.

Hematopoietic reconstitution and safety. The median time to achieve a neutrophil count of 0.5×10^9 /liter was 14 days (range 11–22 days) after the last dose of cyclophosphamide. Patients required a median of 2 units (range 2–5) of packed red blood cells, and a median of 16 days (range 0–23 days) elapsed from the last dose of cyclophosphamide to the last platelet transfusion. Prolonged hospitalization occurred in one patient (for 30 days) with a bacterial sinus infection and in a second patient (for 23 days) with methemoglobinemia precipitated by dapsone. There was no premature ovarian failure; all 11 premenopausal patients maintained menses, with levels of follicle-stimulating hormone in the normal range. In fact, one patient had a successful pregnancy 3 years after treatment with high-dose cyclophosphamide. There were no deaths or fungal infections.

Renal lupus. Baseline data and last followup data for the 9 patients with renal lupus are shown in Table 2. Of these 9 patients, 4 achieved a complete response. Three of the 9 patients were partial responders, and 2 patients had no response. One of the nonresponder patients developed renal failure while receiving high-dose cyclophosphamide and later underwent successful renal transplantation.

Serial measurements of 24-hour urine protein

Table 3. Pre- and posttreatment disease activity markers*

Patient	Diagnosis or organ involvement indicating HDIC (admission date)	PGA, 0-3 VAS		SLEDAI score		Prednisone, mg/day		C3, mg/dl		C4, mg/dl		Anti-dsDNA†	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	CNS, hematologic (6/12/97)	1.5	1	16	4	10	0	64	70	9	5	640	160
2	Renal (10/8/97)	2	0.5	11	2	5	0	61	110	12	9	320	0
3	Renal (7/22/98)	1.5	1	0	4	30	10	124	110	36	37	0	0
4	CNS, pulmonary hypertension (8/21/98)	1	0	10	0	17.5	10	87	95	15	21	0	0
5	CNS, (9/10/98)	2	0.5	8	4	10	5	90	65	19	12	0	160
6	Renal (9/27/98)	2.5	0	4	0	40	0	109	110	23	20	0	0
7	Skin (1/8/99)	2	0.5	2	6	20	10	92	80	22	16	0	10
8	Renal (2/5/99)	2	2	6	4	5	5	104	112	17	17	80	0
9	Renal (2/19/99)	2	0	8	2	60	5	58	124	21	33	80	320
10	Renal (2/26/99)	2	0.5	0	0	5	0	113	116	32	26	0	0
11	Skin (4/7/99)	3	1.5	2	2	40	10	121	148	28	31	0	3.6
12	Renal (6/16/99)	3	1.5	12	6	7.5	5	116	121	28	33	640	40
13	Renal (12/28/99)	2	0.5	8	2	20	5	82	85	5	14	320	160
14	Renal (7/-/00)	2.5	0.5	8	2	9	5	73	93	20	20	20	20

* Patients with renal involvement receive no points on the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) for ongoing proteinuria, even if values are in the nephrotic range. HDIC = high-dose immunoablative cyclophosphamide; PGA = physician's global assessment; VAS = visual analog scale; anti-dsDNA = anti-double-stranded DNA; CNS = central nervous system.

† By *Crithidia luciliae* assay (doubling dilutions) for most patients; in enzyme-linked immunosorbent assay units for patient 11.

excretion for the 9 patients with renal lupus are shown in Figure 1. The pattern in both the partial and complete responders demonstrates gradual improvement over time, with up to 18 months required for maximal improvement. There have been no relapses of disease, with a median followup period of 29 months (range 10-42 months) in responding patients.

Cutaneous lupus. Two patients were treated for severe refractory cutaneous lupus. One patient with skin involvement of 60% of her body surface area had a partial response to high-dose cyclophosphamide (only a few 2-mm lesions remaining on her face), but her disease relapsed at 2 years. The cutaneous relapse then responded to low-dose methotrexate. A patient with severe pyoderma gangrenosum had an initial excellent response followed by relapse which later responded to low-dose cyclosporine (which had previously been ineffective).

CNS SLE. A patient with cerebellar SLE had a complete response to high-dose cyclophosphamide. A second patient with encephalopathy had a complete response of her CNS SLE and her hematologic lupus (pancytopenia). However, 3 years after receiving high-dose cyclophosphamide, she developed proteinuria; renal biopsy showed membranous glomerulonephritis, which has responded to low-dose mycophenolate mofetil.

A third patient with encephalopathy has had a partial response, but still requires IV methylprednisolone approximately once a year for encephalopathy.

She has had improvement of her pulmonary hypertension.

Disease activity measures. A summary of SLE disease activity measures before and after high-dose cyclophosphamide treatment is shown in Table 3. In the total group of 14 patients with refractory lupus, there was a significant improvement in physician's global assessment (mean difference 1.4; $P < 0.0001$), SLE Disease Activity Index (mean difference 4.1; $P = 0.0039$), and prednisone dosage (mean difference 14.9 mg/day; $P = 0.002$). Nine patients were enrolled primarily for renal disease: 4 have had a complete response, 3 have had a partial response, and 2 have had no response. Analysis of all 9 renal SLE patients showed an improvement in physician's global assessment (mean difference 1.4; $P = 0.001$), SLE Disease Activity Index (mean difference 3.9; $P = 0.009$), and prednisone dosage (mean difference 16.3 mg/day; $P = 0.03$). The SLE Disease Activity Index does not add points for ongoing proteinuria, accounting for some of the apparent low activity scores on this instrument. Urine protein declined by dipstick (mean difference 1.94; $P = 0.02$) and by 24-hour excretion (mean difference 3.3 gm/day; $P = 0.01$) (Table 2).

DISCUSSION

In this trial of high-dose cyclophosphamide for refractory SLE, 5 of 14 patients achieved a complete

response, and an additional 6 patients had a partial response, both defined using the RIFLE. Responses were seen in all the organ systems (renal, CNS, and skin) that had involvement leading to patient enrollment. At a median followup of 32 months (range 17–43 months), all complete responses have been durable. In addition, in all 6 partial responders, disease activity has been controlled with immunosuppressive drugs that were ineffective prior to high-dose cyclophosphamide.

High-dose cyclophosphamide was generally well tolerated; common side effects included transient alopecia, nausea, a brief period of aplasia, and febrile neutropenia. The median time to a neutrophil count of $0.5 \times 10^9/\text{liter}$ was 14 days after the last dose of cyclophosphamide, and there was only a median of 10 days (range 8–16 days) with a neutrophil count $<0.5 \times 10^9/\text{liter}$. Importantly, there was no mortality, fungal infection, or mucositis grade >1 in our series. No premature ovarian failure has been seen, in contrast to findings with monthly IV cyclophosphamide.

There are now several reports on the use of high-dose cyclophosphamide therapy followed by stem cell transplantation for autoimmune diseases (9,27). In the majority of these cases, a nonmyeloablative conditioning regimen, usually high-dose cyclophosphamide alone or in combination with other immunosuppressive agents, was employed. We recognize that a direct comparison of autologous stem cell transplant with high-dose cyclophosphamide alone is not appropriate. Without randomized clinical trials, it is not possible to determine whether comparable patients have been enrolled in trials. However, some pertinent issues include hematologic recovery, durable response, and potential toxicity.

Hematologic recovery after high-dose cyclophosphamide without stem cell transplantation is rapid, and complications have been limited. Stem cell transplantation is likely to shorten the duration of aplasia after high-dose cyclophosphamide by only a few days. With stem cell transplant, there is an additional period of aplasia after the autograft-mobilizing dose of cyclophosphamide (i.e., before high-dose cyclophosphamide) that has not been included in the duration of aplasia listed in most reports of autologous stem cell transplantation (6,8,9,28). Thus, the total days of aplasia may be comparable for the two approaches.

Relapses were seen in some patients in our series. Relapses have also occurred in most reported series of autologous stem cell transplantation for severe autoimmune disease (8). Mobilized peripheral blood products usually contain at least 10^9 CD3+ cells, and current

CD34+ selection techniques deplete T cells by only $\sim 3\text{--}4$ logs, which may be unlikely to eliminate autoreactive clones that could reestablish disease with autologous stem cell transplantation. Durable responses have been seen with both high-dose cyclophosphamide and autologous stem cell transplantation (6).

Mortality has been reported with autologous stem cell transplantation (6,28,29), both during stem cell mobilization and after the transplant. However, differences in patient populations (6) rather than differences in the treatment protocols may be the explanation.

High-dose cyclophosphamide without stem cell transplantation warrants further study in severe autoimmune diseases, including SLE. A randomized trial comparing high-dose cyclophosphamide with the National Institutes of Health monthly IV cyclophosphamide regimen in SLE is already under way.

REFERENCES

1. Davis JC, Tassioulas IO, Boumpas DT. Lupus nephritis. *Curr Opin Rheumatol* 1996;8:415–23.
2. Gourley MF, Austin HA III, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis: a randomized, controlled trial. *Ann Intern Med* 1996;125:549–57.
3. McCune WJ, Golbus J, Zeldes W, Bohlke P, Dunne R, Fox DA. Clinical and immunologic effects of monthly administration of intravenous cyclophosphamide in severe systemic lupus erythematosus. *N Engl J Med* 1988;318:1423–31.
4. Boumpas DT, Austin HA III, Vaughan EM, Yarboro CH, Klippel JH, Balow JE. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. *Ann Intern Med* 1993;119:366–9.
5. Bateman H, Yazici Y, Leff L, Peterson M, Paget SA. Increased cervical dysplasia in intravenous cyclophosphamide-treated patients with SLE: a preliminary study. *Lupus* 2000;9:542–4.
6. Burt RK, Traynor AE, Pope R, Schroeder J, Cohen B, Karlin KH, et al. Treatment of autoimmune disease by intense immunosuppressive conditioning and autologous hematopoietic stem cell transplantation. *Blood* 1998;92:3505–14.
7. Brodsky RA, Smith AD. Bone marrow transplantation for autoimmune diseases. *Curr Opin Oncol* 1999;11:83–6.
8. Snowden JA, Brooks PM, Biggs JC. Haemopoietic stem cell transplantation for autoimmune diseases. *Br J Haematol* 1997;99:9–22.
9. Traynor AE, Schroeder J, Rosa RM, Cheng D, Stefka J, Mujais S, et al. Treatment of severe systemic lupus erythematosus with high-dose chemotherapy and haemopoietic stem-cell transplantation: a phase I study. *Lancet* 2000;356:701–7.
10. Karussis DM, Slavin S, Ben-Nun A, Ovadia H, Vourka-Karussis U, Lehmann D, et al. Chronic-relapsing experimental autoimmune encephalomyelitis (CR-EAE): treatment and induction of tolerance, with high dose cyclophosphamide followed by syngeneic bone marrow transplantation. *J Neuroimmunol* 1992;29:201–10.
11. Pestronk A, Drachman DB, Adams RN. Treatment of ongoing experimental myasthenia gravis with short term high dose cyclophosphamide. *Muscle Nerve* 1982;5:79–84.
12. Jacobs P, Vincent MD, Mantel RW. Prolonged remission of severe refractory rheumatoid arthritis following allogeneic bone marrow

- transplantation for drug-induced aplastic anemia. *Bone Marrow Transplant* 1986;1:237-40.
13. Lowenthal RM, Cohen ML, Atkinson K, Biggs JC. Apparent cure of rheumatoid arthritis by bone marrow transplantation. *J Rheumatol* 1993;20:137-40.
 14. Euler HH, Marmont AM, Bacigalupo A, Fastenrath S, Dreger P, Hoffknecht M, et al. Early recurrence or persistence of autoimmune diseases after unmanipulated autologous stem cell transplantation. *Blood* 1996;88:3621-5.
 15. Brodsky RA, Sensenbrenner LL, Jones RJ. Complete remission in severe aplastic anemia after high-dose cyclophosphamide without bone marrow transplantation. *Blood* 1996;87:491-4.
 16. Brodsky RA, Sensenbrenner LL, Smith BD, Dorr D, Seaman PJ, Lee SM, et al. Durable treatment-free remission after high-dose cyclophosphamide therapy for previously untreated severe aplastic anemia. *Ann Intern Med* 2001;135:477-83.
 17. Brodsky RA, Petri M, Smith BD, Seifter EJ, Spivak JL, Styler M, et al. Immunoablative high-dose cyclophosphamide without stem cell rescue for refractory, severe autoimmune disease. *Ann Intern Med* 1998;129:1031-5.
 18. Jones RJ, Barber JP, Vala MS, Collector MI, Kaufmann SH, Ludeman SM, et al. Assessment of aldehyde dehydrogenase in viable cells. *Blood* 1995;85:2742-6.
 19. Sahovic EA, Colvin M, Hilton J, Ogawa M. Role for aldehyde dehydrogenase in survival of progenitors for murine blast cell colonies after treatment with 4-hydroperoxycyclophosphamide in vitro. *Cancer Res* 1988;48:1223-6.
 20. Gordon MY, Goldman JM, Gordon-Smith EC. 4-hydroperoxycyclophosphamide inhibits proliferation by human granulocyte-macrophage colony-forming cells (GM-CFC) but spares more primitive progenitor cells. *Leuk Res* 1985;9:1017-21.
 21. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.
 22. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH, and the Committee on Prognosis Studies in SLE. Derivation of the SLEDAI: a disease activity index for lupus patients. *Arthritis Rheum* 1992;35:630-40.
 23. Petri M, Hellmann D, Hochberg M. Validity and reliability of lupus activity measures in the routine clinic setting. *J Rheumatol* 1992;19:53-9.
 24. Barr SG, Zonana-Nacach A, Magder LS, Petri M. Patterns of disease activity in systemic lupus erythematosus. *Arthritis Rheum* 1999;42:2682-8.
 25. Metropolitan Life Insurance Company. Ideal weights for women. *Stat Bull* 1942;23:6-8.
 26. Metropolitan Life Insurance Company. Ideal weights for men. *Stat Bull* 1943;24:6-8.
 27. Burt RK, Burns W, Hess A. Bone marrow transplantation for multiple sclerosis. *Bone Marrow Transplant* 1995;16:1-6.
 28. Rosen O, Thiel A, Massenkeil G, Hiepe F, Haupl T, Radtke H, et al. Autologous stem-cell transplantation in refractory autoimmune diseases after in vivo immunoablation and ex vivo depletion of mononuclear cells. *Arthritis Res* 2000;2:327-36.
 29. Tyndall A, Gratwohl A. Immune ablation and stem-cell therapy in autoimmune disease: clinical experience. *Arthritis Res* 2000;2:276-80.