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High-Dose Cyclophosphamide Without Stem Cell Rescue for the Treatment of Refractory Behcet's Disease

Charles F. Henderson, MD^{*}, Robert A. Brodsky, MD^{†,‡}, Richard J. Jones, MD^{†,‡}, and Stuart M. Levine, MD^{*}

^{*}Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD

[†]Division of Hematology, Johns Hopkins University School of Medicine, Baltimore, MD

[‡]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD

Abstract

Objective—Behcet's disease (BD) is a systemic inflammatory disorder characterized by recurrent mucocutaneous ulcerations, ocular inflammation, and numerous severe systemic inflammatory manifestations. While most patients respond to standard immunosuppressive therapies, a subset will develop refractory disease. In this report, the use of a novel therapy for the treatment of BD is described.

Methods—Two patients with severe refractory BD who were treated with nonmyeloablative high-dose cyclophosphamide therapy without stem cell rescue.

Results—After treatment, both patients were completely weaned off immunosuppressive therapy and entered disease-free remissions of 18 and 24 months, respectively.

Conclusions—These data suggest high-dose cyclophosphamide therapy without stem cell rescue as an alternative for the treatment of refractory BD.

Keywords

Behcet's disease; vasculitis; cyclophosphamide

Behcet's disease (BD) is a chronic, systemic inflammatory condition of unknown etiology characterized by recurrent oral and genital aphthous ulceration and panuveitis (1,2). Its heterogeneous presentation and often severe systemic manifestations, including necrotizing vasculitis, gastrointestinal ulcerations, aseptic meningitis, and venous and arterial thrombosis (3,4), make the treatment of this condition particularly challenging. Although

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Address reprint requests to: Stuart M. Levine, MD, Johns Hopkins Bayview, Mason F. Lord Building Center Tower, Suite 4100, Room 405, Baltimore, MD 21224. slevine@jhmi.edu.

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often successfully controlled with the use of immunosuppressive medications such as azathioprine, cyclosporine, and TNF-inhibitors, a subset of patients develop severe disease refractory to most currently used therapies (5). High-dose cyclophosphamide therapy without stem cell rescue (HiCy) has recently been employed with success in the treatment of patients with autoimmune hematologic disorders and systemic rheumatic diseases refractory to conventional treatment (6). Its use has not been previously studied for the treatment of BD or other systemic vasculitis syndromes. Here we present 2 patients with BD whose disease continued to progress despite treatment with multiple immunosuppressive regimens who achieved and maintained remissions after treatment with HiCy.

CASE REPORTS

Case 1

The patient is a 51-year-old woman who developed recurrent oral, genital, and gastrointestinal (GI) aphthous ulcers, mild anterior uveitis, erythema nodosum, inflammatory oligoarthritis, and blistering skin lesions on the extensor surfaces of her elbows and knees 12 years earlier. She had a distant history of left lower extremity deep vein thrombosis and possible pulmonary embolism and was treated with Warfarin for 6 months. Based on her presenting symptoms, she met International Study Group criteria for Behcet's disease (7,8) and was started on immunosuppressive medication. Despite several years of treatment with prednisone, hydroxychloroquine, colchicine, and sulfasalazine, she had ongoing cutaneous, ocular, GI, and ocular flares of her disease requiring multiple courses of high-dose intravenous prednisone pulses. She did not tolerate azathioprine due to dose-limiting leukopenia. She was treated with infliximab at a dose of 7.5 mg/kg every 6 to 8 weeks for 3 years with a marked improvement in her symptoms. However, while continuing to receive infliximab therapy, she developed severe recurrent oral and gastrointestinal ulcerations and painful nodular skin lesions requiring multiple hospitalizations for high-dose intravenous corticosteroids. An increase in the infliximab dosing frequency to every 4 weeks and a subsequent switch to adalimumab therapy were not successful in controlling her symptoms. In light of ongoing disease activity and an inability to taper prednisone below 20 mg daily, she was referred for HiCy therapy.

She received cyclophosphamide 200 mg/kg IV divided over 4 consecutive days. Her course was complicated by transient pancytopenia, which resolved within 3 weeks following her infusions. All cutaneous, GI, and mucocutaneous manifestations of her disease rapidly subsided; her steroids were rapidly tapered to off within 3 months of the HiCy infusions therapy, and she has remained in clinical remission off of all immunosuppressive therapy 2 years later.

Case 2

The patient is a 30-year-old woman who developed recurrent nonherpetic aphthous genital ulcers at age 15 and oral aphthous ulcers at age 17, with associated inflammatory oligoarthritis and ulcerative skin lesions. She developed bilateral anterior and posterior uveitis, retinal vasculitis, and ciliochoroidal detachment at age 18 and was treated with high-dose prednisone and methotrexate. Due to refractory uveitis, both mycophenylate mofetil

and cyclosporine were tried, but were discontinued due to adverse reactions. At age 20, she developed an inflammatory brainstem mass successfully treated with high-dose corticosteroids. Her ophthalmologist made the diagnosis of BD based on International Study Group criteria when she was 21 years old and she was treated with cyclophosphamide infusions at a dose of 750 mg/m² every 2 to 3 weeks for the next 18 months in addition to high-dose oral corticosteroid therapy. Over the next 4 years, she experienced several more flares of her uveitis requiring hospitalization, IV cyclophosphamide, and pulse steroids. Her disease was relatively quiescent for the next 2 years, but she then experienced recurrent uveitis, new CNS lesions on follow-up imaging, recurrent ulcers, and arthritis requiring the introduction of azathioprine and prednisone, and the eventual addition of infliximab up to a dose of 7.5 mg/kg every 8 weeks. After 8 months on this regimen, she had persistent oral and genital ulcers and uveitis.

Due to the refractory nature of her disease and her previous treatment with conventional doses of cyclophosphamide, she was referred for HiCy treatment. She received cyclophosphamide 200 mg/kg IV divided over 4 consecutive days, and her postinfusion course was complicated by 1 episode of neutropenic fever, and episodes of both pneumonia and *Clostridium difficile* colitis. Treatment-related thrombocytopenia and anemia occurred, but were transient; recovery of the platelet count to levels above 50,000/ μ L and hemoglobin above 10 mg/dL was observed by day 14. Her uveitis resolved within 3 months of her infusions, and her visual acuity improved from nearly absent on the right and 20/100 on the left to 20/30 pinhole corrected on the right and 20/50 on the left. Over the next 8 months of follow-up her prednisone was successfully discontinued without further sequelae of her disease. Now at age 30, she has not had any recurrence of uveitis, mucocutaneous ulcerations, or neurologic symptoms in the 18 months following her cyclophosphamide infusions, and her previously documented CNS lesions have completely resolved on follow-up imaging.

DISCUSSION

We report here the use of nonmyeloablative HiCy for the treatment of severe Behcet's disease in 2 patients who were refractory to, or intolerant of, standard immunosuppressive treatments. This is the first reported use of this therapy in patients with BD. The results were rapid, with both patients achieving complete clinical remission within 3 months of receiving HiCy therapy. In both cases, the adverse effects were manageable and non-life-threatening and comparable to those seen in previous HiCy studies (9–11). This regimen was first successfully used in the treatment of severe aplastic anemia over a decade ago (12). Its clinical utility for the treatment of severe autoimmune disease is defined by its ability to generate immunoablation in the absence of complete myeloablation, thereby obviating the need for hematopoietic stem cell rescue following treatment. This is because pluripotent hematopoietic stem cells are resistant to cyclophosphamide due to their high expression of the cyclophosphamide-metabolizing enzyme aldehyde dehydrogenase (13). As a result, HiCy followed by natural immune reconstitution is believed to generate a renewal of self-tolerance through the destruction of more differentiated autoreactive lymphocytes and their precursors, which unlike stem cells, are highly sensitive to this therapy (6,14). Since its initial application to the treatment of severe aplastic anemia in 1996 (12), HiCy has been

successfully used in the treatment of a variety of organ-limited and systemic autoimmune diseases including systemic lupus erythematosus, scleroderma, multiple sclerosis, myasthenia gravis, pemphigus vulgaris, and others (10,11,14–16). Aside from its effects on cellular immunity, HiCy has also been shown to eradicate auto- and alloantibody titers following treatment, a phenomenon accounting for its utility in the treatment of antibody-mediated autoimmune cytopenias (17).

The rationale for using this regimen in our patients was supported by previous reports among 6 patients treated with high-dose chemotherapy for the treatment of refractory BD (Table 1) (18–21). In these cases, partial or complete remissions were experienced in all cases using both myeloablative and nonmyeloablative conditioning regimens followed by autologous or allogeneic hematopoietic stem cell rescue to hasten hematologic recovery. Strikingly, dramatic responses were seen in each case, including in patients with severe refractory gastrointestinal, pulmonary, and neurologic manifestations.

Although therapeutically successful for BD and other systemic autoimmune diseases (22,23), the chemotherapy/ stem cell rescue protocols utilized in these studies have several important drawbacks, including the following: (1) the use of multi-agent conditioning regimens; (2) costly and cumbersome peripheral stem cell mobilization procedures; (3) the risk of re-infusing unpurged autoreactive lymphocytes during the stem cell rescue procedure; and (4) for allogeneic stem cell rescue, the risk of acute graft-versus-host disease and the need for maintenance immunosuppression following the procedure (6). HiCy offers several notable advantages over these regimens. These include the simplicity and manageable side effect profile of a single-agent regimen, the elimination of stem cell mobilization protocols, elimination of the risk of re-introducing autoreactive clones, and lower overall costs of the procedure (24). Further, there is little evidence that the addition of stem cell rescue following high-dose cyclophosphamide therapy hastens hematologic recovery, reduces the need for transfusions, or reduces mortality (24). However, no direct comparative studies of nonmyeloablative cyclophosphamide with and without stem cell rescue for the treatment of severe systemic autoimmune disease have been performed to date.

Although numerous therapies have been shown to be efficacious for the treatment of BD, the therapeutic options for patients with severe, refractory, and organ-threatening disease are limited (5). The data presented here reveal that HiCy might represent an attractive therapeutic alternative in patients with severe disease. Since our initial follow-up is limited to 18 and 24 months, respectively, we cannot comment on the ability of HiCy therapy to induce long-term durable remissions beyond this timeframe in patients with BD. However, long-term follow-up studies in patients with aplastic anemia treated with HiCy reveal sustained response rates of up to 70% at 10 years (25), suggesting that long-term durable responses are possible following this treatment. Future prospective studies in appropriately selected patients will need to be performed to determine the optimal application of HiCy treatment in BD and other systemic vasculitides.

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Reported Experience of High-Dose Chemotherapy with Bone Marrow Rescue in Severe Behcet's Disease

Table 1

No.	Patient	Dominant Phenotype	Treatment	Prevention of GVHD	Remission Status	Current tx	F/U	Reference
1	32 yr old M	Pulmonary	MPH, autologous SCT	N/A	Complete	None	5 yr	18
2	49 yr old M	Pulmonary	MPH, autologous SCT	N/A	Partial	Pred 8 mg/d	5 yr	18
3	4 yr old F	Gastrointestinal	CYC/FLD/ATG, autologous SCT	N/A	Complete	None	2 yr	19
4	34 yr old F	Neurologic	1. BEAM + ATG, autologous SCT 2. Thio-Tepa/CYC, allogeneic SCT	1. N/A 2. MTX and CSA	90 days 2 years	N/A None ^a	N/A 2 yr	20 20
5	23 yr old M	Neurologic	BEAM, autologous SCT	N/A	Complete	None	48 mo	21
6	22 yr old M	Neurologic	BEAM, autologous SCT	N/A	Complete ^b	None	48 mo	21

MPH, melphalan; SCT, stem cell transplant; CYC, cyclophosphamide; FLD, fludarabine; CSA, cyclosporine; MTX, methotrexate; ATG, anti-thymocyte globulin; BEAM, BCNU/Etoposide/Ara-C/Melphalan.

^aGVHD prophylaxis only.

^bResidual fixed neurologic deficit.