Table 1. Response to twice-daily subcutaneous bolus injections of deferoxamine: update of old and new cases

Patient no.*	Diagnosis	Age, y/sex	Initial ferritin level, μg/L†	TIL before chelation, mg/kg‡	TIL during chelation, mg/kg‡	UIE after DFO bolus, μg/48 h	UIE after DFO infusion, μg/48 h	Follow-up time, mo	Last ferritin value, μg/L
4	IMF	61/M	2100	261.0	316.1	7880	11 530	74	816
6	CML, CP	48/F	1670	195.8	427.2	13 000	11 390	79	550
7	NHL, LG	77/F	1130	95.2	419.0	4144	3737	78	670
8	MDS, RA	51/F	685	89.8	422.7	7703	6790	81	522
17	MDS, RAS	63/F	2153	232.0	360.5	11 050	13 480	72	1120
28	MDS, RA	57/F	1466	110.7	192.0	8728	10 218	38	710
29	MDS, RAEB-t	76/M	3592	255.1	158.4	4256	2880	35	1912
30	MDS, RA	45/M	1875	129.4	118.4	11 010	8860	21	1235
31	MDS, RA	64/M	2510	174.0	94.1	7010	3900	12	1930
32	MDS, RAEB	63/F	829	83.1	126.7	9870	13 220	26	435
33	MDS, RAEB	59/M	1254	96.7	101.3	6190	5310	13	630
34	RCA	55/F	781	77.0	226.1	3330	3412	51	432
Mean (± SD)			1670.3 (± 843.9)	150.0 (± 70.1)	246.9 (± 134.0)	7847.6 (± 3047.6)	7893.9 (± 4019.3)	46.8 (± 28.9)	913.5 (± 532.0)

UIE indicates urinary iron excretion; IMF, idiopathic myelofibrosis; MDS, myelodysplastic syndrome; RA, refractory anemia; RAS, refractory anemia with ring sideroblasts; RAEB, refractory anemia with excess of blast cells; RAEB-t, refractory anemia with excess of blast cells in transformation to AML; CML, chronic myeloid leukemia; CP, chronic phase; NHL, non-Hodgkin lymphoma; LG, low grade; TIL, transfusional iron load; and RCA, red cell aplasia.

*Patient nos. 4, 6, 7, 8, 17 are old cases; patient nos. 28-34 are new cases.

†Normal range of serum ferritin concentration: 15 μg/L to 250 μg/L.

‡Transfusional iron load (TIL) before chelation therapy (expressed as the total amount of iron transfused per kilogram of body weight) and TIL during chelation therapy (expressed as the total amount of iron transfused during the follow-up time [months] per kilogram of body weight).

infusion of DFO. The data from the 5 patients who remained in the study, together with data from 7 additional cases, are shown in Table 1. We did not record any adverse events in the 7 new cases, after a median follow-up of 28 months. As regards the second group of 11 transfusion-independent patients, 3 patients (patient nos. 16, 23, and 27) died due to progression/relapse of disease and 2 patients (patient nos. 18 and 26), who are still alive, came out of the protocol because they restarted chemotherapy due to relapse of the hematologic malignancy. In the remaining 6 patients (patient nos. 11, 13, 20, 21, 24, and 25), the twice-daily subcutaneous bolus injections of DFO normalized ferritin levels. In these patients, who did not require transfusions during the follow-up after chemotherapy, DFO bolus injections were stopped once normal ferritin levels had been reached. The ferritin levels were then monitored every 3 months. Patient number 20 (with spherocytosis and hereditary hemochromatosis) started a maintenance phlebotomy program with bolus injection of DFO due to an increase of serum ferritin levels (780 μg/L).

Although the newly reported cases further testify to the efficacy of this method, there are some concerns regarding the long-term tolerance of DFO bolus injections. In fact, examining the follow-up of the previously published cases, we found that 3 of the 8 patients who remained in the study did not tolerate the volume of the bolus injections, preferring the subcutaneous continuous infusion. The pharmaceutical company producing DFO recommends a 10% final concentration of the drug, because higher concentrations have been shown to be associated with a higher incidence of local reactions at the injection site.[10]

Long-term follow-up trials on larger populations of patients are needed in order to clarify the real incidence of adverse reactions in patients using twice-daily subcutaneous bolus injections of deferoxamine.

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To the editor:

Autologous hematopoietic stem cell transplantation for severe/refractory intestinal Behcet disease

Behcet disease is a chronic inflammatory disorder of unknown etiology characterized by recurrent oral aphthous ulcers, genital ulcers, skin lesions, and uveitis.[1] It has long been postulated that immunologic abnormalities, which are possibly triggered by microbial pathogens in genetically susceptible individuals (strong association with HLA-B51), are important in its pathogenesis.[2] Recent

Table 1. Immune reconstitution after ASCT

	1 mo after ASCT	2 mo after ASCT	4 mo after ASCT	12 mo after ASCT	Reference value in healthy child
$CD3^+$ cells/μL	40	310	485	1675	1020-4160
$CD4^+$ cells/μL	10	25	105	985	525-2860
$CD8^+$ cells/μL	28	320	410	1035	350-2100
$CD19^+$ cells/μL	10	170	210	600	100-780
Proliferative response to PHA, cpm	1250	3000	12 115	28.900	20 000-47 000
Proliferative response to concanavalin-A, cpm	285	4250	9760	13.345	12 000-21 000
Proliferative response to OKT3, cpm	670	1350	29 778	41.980	30 000-52 000
NK activity: target-effector ratio 10:1, %	6	8	16	15	10-20
NK activity: target-effector ratio 30:1, %	12	22	31	24	17-32
NK activity: target-effector ratio 100:1, %	23	41	64	48	28-52
IgG, mg/dL	180	250	350	745	593-1723
IgM, mg/dL	20	25	40	190	36-314
IgA, mg/dL	< 5	< 5	25	110	33-235

The patient experienced profound immune impairment of immune function during the first 4 months after the lymphocyte-depleted ASCT. Progressive recovery of both lymphocyte number and of proliferative response to polyclonal activators occurred over time. Detectable natural killer (NK) activity was already present after the first few months following transplantation. Response to nominal antigens (ie, *Candida albicans* and HCMV) was observed only 9 to 12 months after ASCT (data not shown).

findings have better defined the nature of inflammation, revealing the central role of T-cell–mediated immunity. Histopathologic and laboratory investigations have demonstrated mainly T-cell–dominated perivascular infiltrates in involved tissue, with presence in the blood of aberrant oligoclonal polarized Th1 T-cell population (in particular, γδ T cells producing tumor necrosis factor α [TNFα]).[3,4] To date, Behcet disease is recognized as a multisystem vasculitis, which can also affect all types and sizes of blood vessels in joints, lungs, central nervous system, and gut.[2]

Few patients with Behcet disease have gastrointestinal ulceration. Such patients, in particular those with diffuse ulceration, are very difficult to treat and have higher mortality as a result of severe complications.[5] Surgery is required in cases involving complications (perforation) and failed medical treatment (persistent bleeding), but it is often palliative, with postsurgical recurrence occurring in about 75% of patients.[6] We describe the successful treatment of a child with severe/refractory intestinal Behcet disease, by lymphocyte-depleted autologous stem cell transplantation (ASCT) following high-dose immunosuppressive therapy (HDIT). The rationale for HDIT lies on the hypothesis that a vigorous immunoablative regimen can delete the autoaggressive lymphocyte clones, thus allowing the "reset" of the immune system, with recapitulation of ontogenesis and, potentially, development of tolerance toward self antigens. However, as complete eradication of autoimmunity has yet to be proven, a less ambitious and more realistic hypothesis is that an intensive immunosuppressive regimen may, through modulation of the immune response, induce prolonged remission and favorably affect the natural course of the disease.

A 4-year-old girl presented with recurrent episodes of fever, aphtoid oral ulcers, papulopustolar and Sweet syndrome–like skin lesions, arthralgias, conjunctivitis, and gastrointestinal symptoms (abdominal pain, bloody diarrhea, and weight loss). Pathergy test was positive. Autoantibodies were negative. Colonoscopy revealed serpiginous and aphtoid ulceration in descending, transverse, and ascending colon, as well as shallow ulcers in the terminal ileum. Biopsies demonstrated chronic inflammatory infiltrate in the lamina propria and submucosa with focal lymphoid aggregates, without granulomas. For 2 years the child underwent several medical therapeutic attempts consisting of total parenteral nutrition with bowel rest, intravenous bolus of high-dose metyl-prednisolone and oral prednisone associated with sulfasalazine, azathioprine, cyclosporin, tacrolimus, methotrexate, and cyclophosphamide. Unfortunately, disease recurrence occurred after each attempt to reduce the dose of oral steroid. Faced with refractory symptoms, we tried to induce remission with 4 cycles of anti-TNFα monoclonal antibody infliximab,[7] but the result was disappointing with transient response. Given the high risk of developing complications and the poor prognosis associated with diffuse intestinal involvement, we decided to intensify immunosuppression with high-dose chemotherapy followed by ASCT.[8] Recent studies have shown that conditioning regimens for severe autoimmune disease using high-dose cyclophosphamide alone (200 mg/kg) are not myeloablative and do not necessarily require stem cell rescue.[9] However, in view of the extreme refractoriness of the disease, we decided to use a more powerful immunoablative regimen, followed by infusion of hematopoietic stem cells, able to accelerate hematologic recovery, thus reducing the risk of infectious complications.

Moreover, due to the peculiar presence of oligoclonal aberrant T cells in peripheral blood of patients with Behcet disease, we reasoned that an immunologic "purging" of lymphocytes contained in the autograft would be expected to significantly diminish the risk of reinfusion of such autoreactive cells and, thus, of disease relapse. After the patient had received cyclophosphamide at a dose of 2 g/m^2 and granulocyte colony-stimulating factor (G-CSF) at a dose of 8 μg/kg per day for 5 days, we collected stem cells, which were subsequently enriched ex vivo for $CD34^+$ cells (positive selection). The conditioning regimen consisted of cyclophosphamide 100 mg/kg, fludarabine 160 mg/m^2, and antithymocyte globulin (ATG) 60 mg/kg. The total number of $CD34^+$ cells infused was 11×10^6/kg, whereas the residual T and B lymphocytes infused were 3×10^3/kg and 4×10^4/kg, respectively. Neutrophil ($> 0.5 \times 10^9$/L) and platelet ($> 50 \times 10^9$/L) engraftment occurred on day +9 and day +14, respectively. The posttransplant course was substantially uneventful. Monitoring of Epstein-Barr virus and cytomegalovirus reactivation by polymerase chain reaction and antigenemia, respectively, always resulted negative. The patient immune function was monitored over time; after having profound immune impairment during the first 4 months after transplantation, the patient progressively recovered both lymphocyte number and function (Table 1). Despite discontinuation of therapy with prednisone, the child experienced a marked improvement of her general well-being, with complete resolution of all signs and symptoms. Coloscopy revealed complete healing of the lesions. Two years after undergoing transplantation, the child is still in complete, medication-free remission. Although the follow-up is relatively

short, we may conclude that highly immunosuppressive, lymphocyte-depleted ASCT is a useful and safe therapy for the intractable form of intestinal Behcet disease.

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