Am J Blood Res 2013;3(1):84-90
www.AJBlood.us /ISSN:2160-1992/AJBR1212002

*Original Article*

# Repeated treatment with high dose cyclophosphamide for severe autoimmune diseases

Amy E DeZern[1], Michael J Styler[2], Daniel B Drachman[3], Laura K Hummers[4], Richard J Jones[1], Robert A Brodsky[5]

*[1]Division of Hematologic Malignancies, Department of Medical Oncology, The Johns Hopkins School of Medicine; [2]Division of Hematology/Oncology, Department of Medicine, Drexel University College of Medicine; [3]Department of Neurology, The Johns Hopkins School of Medicine; [4]Division of Rheumatology, Department of Medicine, The Johns Hopkins School of Medicine; [5]Division of Hematology, Department of Medicine, The Johns Hopkins School of Medicine, Baltimore, MD, USA*

Received December 5, 2012; Accepted January 3, 2013; Epub January 17, 2013; Published January 25, 2013

**Abstract:** High dose cyclophosphamide (HiCY) without stem cell rescue has been shown to induce remissions in patients with severe autoimmune disorders (SADS). However, up to 80% of these patients ultimately relapse. Here we review the outcomes of seven patients treated with two cycles and one patient treated with three cycles of HiCY. The diseases re-treated were scleroderma, multiple sclerosis, three patients with severe aplastic anemia (SAA), and three patients with myasthenia gravis (MG). All but two patients with SAA had received standard immunomodulatory therapy for their disease up front and had been refractory. All patients had complete hematologic recovery. Overall survival in this cohort was 100%. All patients relapsed after the initial cycle but event free survival thereafter was 93.3%. All are still in remission except two MG patients, one of whom relapsed after a severe GI infection requiring hospitalization, and the other relapsed 3 years after the second treatment and she did not respond to the third treatment. This shows that HiCY can be safely re-administered in patients with SAA and refractory SADS. The quality and duration of second remissions appears to be equal or superior to the first remission.

**Keywords:** Autoimmunity, cyclophosphamide, severe autoimmune diseases

## Introduction

High dose cyclophosphamide (HiCY) is highly effective for treating severe aplastic anemia (SAA) [1, 2] and a variety of refractory severe autoimmune diseases including myasthenia gravis [3], multiple sclerosis [4], scleroderma [5], lupus [6], autoimmune hemolytic anemia [7] and others [8, 9]. Cyclophosphamide's pharmacology is responsible for its differential toxicity against the immune system without damaging hematopoietic stem cells [10]. Cyclophosphamide is a prodrug that is converted by the liver to 4-hydroxycyclophosphamide and aldophosphamide, bloodstream intermediates that are ultimately converted to phosphoramide mustard. The major mechanism of cyclophosphamide degradation is inactivation of aldophosphamide by cellular aldehyde dehydrogenase to form the inert compound carboxyphosphamide [11]. Hematopoietic stem cells are resistant to cyclophosphamide because they express elevated levels of aldehyde dehydrogenase [12]. Lymphocytes have low levels of aldehyde dehydrogenase and are rapidly killed by HiCY; therefore, HiCy is highly immunosuppressive but not myeloablative.

In patients with SAA treated with HiCY, overall survival, response rate, and event free survival at 10 years is 88%, 71% and 58%, respectively, in previously untreated patients [2]. SAA patients who are refractory to conventional immunosuppressive therapy (e.g, antithymocyte globulin and cyclosporine) have lower response rates to salvage therapy with HiCY; however, durable responses have been reported in over 25% of patients with refractory SAA [2]. HiCY has also been used in a variety of refractory severe autoimmune disease (SADS) including lupus, multiple sclerosis, myasthenia gravis, scleroderma, autoimmune hemolytic

anemia, and others. The response rate in these conditions exceeds 90%; however, most patients with SADS ultimately relapse following HiCY therapy with only 20% remaining disease-free at 5 years after HiCY therapy [9]. Although not permanent, these remissions are often clinically valuable, since many patients become asymptomatic and are able to discontinue corticosteroids and other toxic immunosuppressive medications for several years. While initially conceived as a one-time therapy, we have now re-treated several patients with HiCY. Here, we demonstrate that HiCY can be safely re-administered in patients with SAA and refractory SADS. Importantly, the quality and duration of second remissions appears to be equal or superior to that of the first remission.

## Materials and methods

From 2000-2012 the records of the Johns Hopkins Hospital were reviewed for patients with various autoimmune diseases treated with one or more courses of high dose cyclophosphamide. Some of the patients have previously been included in reports of their initial treatments. All protocols were approved by the Institutional Review Board of Johns Hopkins, and all participating patients (or their guardians) provided written informed consent. Patients were recruited from the hematologic, neurologic, or rheumatologic clinics of the Johns Hopkins Hospital, Baltimore, Maryland. One patient was treated at Hahnemann University for access of care issues.

### *Treatment schedule*

High-dose cyclophosphamide (50mg/kg) was administered intravenously over one hour through a central venous catheter on four consecutive days. The dose of cyclophosphamide was based on the lesser of actual or ideal body weight as determined by the Metropolitan Life table. Intravenous mesna (10mg/kg) was administered 30 minutes before, and then 3, 6, and 8 hours after, cyclophosphamide as prophylaxis against hemorrhagic cystitis. Beginning six days after the last dose of cyclophosphamide, patients received granulocyte colony stimulating factor (5 μg/kg/day) until the absolute neutrophil count exceeded 1.0 x $10^9$/liter. This was done identically with each subsequent treatment as well as the initial treatment.

### *Supportive care*

A serotonin 5-HT3 receptor antagonist such as ondansetron (32 mg) was administered intravenously before each dose of cyclophosphamide. Prophylactic antimicrobial support, consisting of fluconazole (400 mg/day), norfloxacin (400 mg/day)(except in MG patients) and valacyclovir (500 mg twice per day, if antibodies to herpes simplex virus were present), was given beginning on the day after the last dose of cyclophosphamide and continued until the neutrophil count exceeded 0.5 x $10^9$/liter. *Pneumocystis* prophylaxis (usually trimethoprim-sulfamethoxazole or dapsone) was administered for 6 months. Packed red blood cell (leukocyte poor) transfusions were administered to maintain a hematocrit level > 25%. Platelet transfusions were administered to maintain a platelet count > 10 x $10^9$/ liter, and for bleeding and procedures.

### *Statistical analysis*

Complete response (or disease improvement) was defined here as a decrease in disease activity in conjunction with a decrease or elimination of immune modulating drugs. Definitions of disease activity varied by disease and have been previously reported. Relapse was defined as worsening disease activity and/or a requirement for an increase in dose of, or administration of new, immunosuppressive medications. This was the trigger for re- treatment. Hospital days were determined from initial hospitalization for the cyclophosphamide dosing and then any subsequent inpatient time for neutropenic fever or other complications. The patients were seen in the outpatient transplantation clinic seven days a week through the period of neutropenia, and antibiotics and blood products were administered as necessary. This is included in total treatment days.

## Results

### *Patient characteristics*

A review of all 150 patients treated with high dose cyclophosphamide (HiCY) between January 2000 and August 1, 2012 showed seven patients treated with two cycles of HiCY and one patient treated with three cycles. All but two patients with SAA had received standard immunomodulatory therapy for their dis-

**Table 1.** Patient Characteristics and Response Details

| | Tx # | Patient age at treatment (years) | Days ANC <500 ( / cu mm) | Platelet Transfusions (n= pheresis units) | Days to Plt independence | PRBC Transfusions (n=units) | Days to PRBC independence | Total days of treatment (inpatient or outpatient) | Response | Length of Response (months) | Total follow up time from first dose of HiCY (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient A | Male with aplastic anemia | | | | | | | | | | |
| | 1 | 44 | 36 | 9 | 20 | 6 | 14 | 69 | CR | 70 | |
| | 2 | 50 | 36 | 15 | 21 | 11 | 19 | 81 | CR | 63 | 141 |
| Patient B | Male with aplastic anemia | | | | | | | | | | |
| | 1 | 17 | 66 | 37 | 56 | 40 | 56 | 31 | CR | 60 | |
| | 2 | 21 | 154 | 88 | 156 | 90 | 156 | 54 | CR | 64 | 124 |
| Patient C | Male with aplastic anemia | | | | | | | | | | |
| | 1 | 19 | 28 | 11 | 29 | 16 | 25 | 31 | CR | 57 | |
| | 2 | 24 | 32 | 11 | 33 | 18 | 35 | 35 | CR | 45 | 108 |
| Patient D | Male with scleroderma | | | | | | | | | | |
| | 1 | 19 | 11 | 3 | 11 | 2 | 9 | 27 | CR | 22 | |
| | 2 | 21 | 18 | 9 | 23 | 6 | 18 | 41 | CR | 49 | 80 |
| Patient E | Female with multiple sclerosis | | | | | | | | | | |
| | 1 | 30 | 7 | 0 | N/A | 0 | N/A | 23 | CR | 24 | |
| | 2 | 32 | 10 | 0 | N/A | 2 | 18 | 23 | CR | 33 | 67 |
| Patient F | Female with myasthenia gravis | | | | | | | | | | |
| | 1 | 27 | 6 | 3 | 12 | 6 | 10 | 29 | CR | 72 | |
| | 2 | 33 | 9 | 2 | 11 | 1 | 10 | 30 | CR | 29 | 129 |
| Patient G | Female with myasthenia gravis | | | | | | | | | | |
| | 1 | 35 | 8 | 3 | 12 | 2 | 14 | 23 | CR | 108 | |
| | 2 | 46 | 8 | 2 | 15 | 2 | 16 | 23 | CR | 30 | 151 |
| Patient H | Female with myasthenia gravis | | | | | | | | | | |
| | 1 | 40 | 13 | 5 | 16 | 6 | 19 | 25 | CR | 35 | |
| | 2 | 43 | 13 | 7 | 16 | 6 | 15 | 32 | CR | 36 | |
| | 3 | 46 | 13 | 1 | 11 | 2 | 14 | 36 | NR | 0 | 104 |

Abbreviations: N/A not applicable; ANC absolute neutrophil count; CR complete response; NR no response.

ease and were refractory to standard treatment prior to the initial treatment with HiCY. The male to female ratio was 1:1. The diseases retreated were scleroderma, multiple sclerosis, three patients with SAA, and three patients with myasthenia gravis. The median time between HiCY treatments was 40 months (range, 26-122 months). The median age of initial treatment with HiCY was 28.5 years (range, 17-40 years) and median age on retreatment was 32.5 (range, 21-50) years. The median follow up time from initial HiCY treatment to present was 108 months (Range 67-141). **Table 1** outlines the features of each individual patient.

*Toxicity*

There were few unexpected side-effects. [3, 5, 7, 13, 14] Nausea with or without emesis during the treatment period was managed with intravenous and oral antiemetics. All patients experienced temporary alopecia and pancytopenia. Febrile neutropenia requiring admission to the hospital occurred in all patients but one with both treatments. The single patient that did not have a neutropenic fever was fever free on both treatments. The causes of fever with readmission were appendicitis in one AA patient and MRSA bacteremia (in another AA patient), disseminated fungal infection and parvovirus infections. The latter two were aplastic anemic patients who had more prolonged periods of neutropenia than the patients with other diseases.

*Hematopoietic recovery*

Hematopoietic recovery occurred in all patients. As expected, the three patients with aplastic anemia had longer times to recovery than did the five patients with autoimmune diseases that do not target the bone marrow. In all patients time to hematopoietic recovery after their second course of Hi Cy was similar to the time after their initial HiCY treatment, except for patient B (SAA). The median duration of neutropenia for all patients was 11 (range 6-66) days after the initial cycle and 13 (range 8-154) days after the retreatment cycle. Hematopoietic recovery was more rapid in patients without SAA with a median duration of neutropenia of 8 days after cycle one and 11.5 days after cycles 2 or more.

The median time to the last packed red blood cell transfusion after completion of HiCY for all patients was 15 days (range 0-156) and the median time to the last platelet transfusion was 16 days (range 0-156 days). The median number of packed red blood cell transfusions was 6 (range 0-90) and the median number of platelet transfusions was 5 (range 0-88). The patients with SAA had a median of 25 days after HiCY to red cell independence after cycle one and 35 days after cycle 2. The patients with other autoimmune diseases had a median of 10 days after HiCY to red cell independence after cycle one and 14.5 days after cycles 2 or 3. The patients with SAA had a median of 29 days after HiCY to platelet independence after cycle one and 33 days after cycle 2. The patients with other autoimmune diseases had a median of 12 days after HiCY to platelet independence after cycle one and 11.5 days after cycles 2 or 3.

*Response*

The overall response rate to HiCY was 94.1% across all 17 cycles represented here. All patients responded after the first and second treatments. The single patient treated three times did not respond to the third treatment. Patients C, F, and G have shorter follow-up after their second cycle of HiCY compared to their first; however, the remaining patents have achieved a second remission that is comparable or even greater in duration than their first complete remission (CR). The response criteria were detailed for each disease and the individual provider for the disease of interest. In the patient with multiple sclerosis, her response was defined as at least a 1 point improvement on the Expanded Disability Status Scale. [15] The SAA patients' response was defined by transfusion independence and near normalization of blood counts for age and sex. The myasthenia patients' responses were defined by improvement in myasthenia gravis disease activity score [16] as well as their Karnofsky performance scores [17]. The disease specific details of each response can be seen in **Table 2**.

*Overall and event-free survival*

Overall survival in this cohort was 100%. All patients relapsed after the initial cycle but event free survival thereafter was 93.3%. All are still in remission except the MG patient treated for a third time who did not respond to the third treatment. Patient F remained in remission after her second HiCY treatment for

**Table 2.** Disease specific details of response to HiCY

| | Treatment at time of #1 HiCy | Disease severity at time of #1 HiCy | Response post #1 HiCy | Treatment at time of #2 HiCy | Disease severity at time of #2 HiCy | Response post #2 HiCy |
|---|---|---|---|---|---|---|
| Patient A | ATG/ CSA x 2 | ANC 540<br>Hb 8.3<br>Plts 16 | ANC 2600<br>Hb 14.7<br>Plts 111 | None | ANC 470<br>Hb 7.3<br>Plts 14 | ANC 3050<br>Hb 15.6<br>Plts 112 |
| Patient B | Growth factors | ANC 30<br>Hb 7.6<br>Plts 6 | ANC 2880<br>Hb 16.9<br>Plts 124 | None | ANC 840<br>Hb 9.1<br>Plts 7 | ANC 2050<br>Hb 14.6<br>Plts 103 |
| Patient C | None | ANC 680<br>Hb 3.4<br>Plt 11 | ANC >2500<br>Hb >15<br>Plts >150 | None | ANC 800<br>Hb 6.8<br>Plts 11 | ANC >2500<br>Hb >15<br>Plts >150 |
| Patient D | Pred 7.5; MTX | mRSS 28 | mRSS 4<br>off all IST | CY | mRSS 32 | mRSS 0<br>off all IST |
| Patient E | IFN | EDSS 6.5 | EDSS 1.5<br>off all IST | Glatiramer acetate | EDSS 3.0 | EDSS 1.0<br>off all IST |
| Patient F | Pred 50; MMF; Pyr; pheresis q 30 days; tacrolimus | KPS 80<br>MG IVb | KPS 100<br>MG 0 | Pred 40; Pyr; pheresis q7days | KPS 55<br>MG IVb | KPS 100<br>MG 0 |
| Patient G | Pred 60; CsA; Pyr | KPS 40<br>MG IVb | KPS 100<br>MG I | Pred 60; Pry; pheresis q7days | KPS 60<br>MG IVb | KPS 100<br>MG 0 |
| Patient H | Pred 80; MMF; Pyr;IVIg | KPS 40<br>MG V | KPS 100<br>MG 0 | Pred 50; MMF; Pyr;IVIg; tacrolimus; pheresis q4days<br>Had to resume same regimen prior to #3 HiCy | KPS 60<br>MG V<br>#3 HiCY:<br>KPS 40<br>MG V | KPS 100<br>MG 0<br>#3 HiCY:<br>KPS 70<br>MG V |

Abbreviations: IST immunosuppressive therapy; ANC Absolute neutrophil count; Hb Hemoglobin; Plts Platelets; CY Cytoxan (oral); CsAcyclosporine; Pred Prednisone with daily dosage in mg; Pyr Pyridostigmine; IVIG Intravenous immunoglobulin; IFN interferon Beta IA; mRSS modified Rodnan skin score; KPS Karnofsky Performance Score; EDSS Expanded Disability Status Scale; MTX methotrexate; ATG Antithymocyte globulin; MMF mycophenolate mofetil; MG Maximum score on Myasthenia Gravis Foundation of America scale.

29 months. During that time, she was maintained on low dose prednisone (10 mg every other day) and Mycophenolate mofetil, but then stopped the Mycophenolate mofetil because she was trying to conceive. She then had a gastrointestinal infection that resulted in vomiting and required hospitalization, and then had a relapse of MG. She was maintained with repeated plasma exchanges until August 2012, when she was treated with rituximab (1 gram on two occasions). The MG has remained asymptomatic during the 3 months since the rituximab treatment.

## Discussion

High dose cyclophosphamide induces remissions in patients with SAA and other autoimmune disorders. [9] The safety of this approach has been demonstrated and does not require human stem cell transplantation. Most remissions in patients with SAA are durable, but the relapse rate in patients with other refractory severe autoimmune disease such as myasthenia gravis, scleroderma and multiple sclerosis is much higher. Here, we demonstrate that repeat treatment with HiCY is safe and feasible. Moreover, the toxicity and quality of response appear to be comparable, and in some cases superior in duration to that of the initial HiCY treatment. As previously reported, the duration of aplasia was significantly longer in patients with SAA than in patients with other refractory severe autoimmune disease that did not involve the bone marrow.

HiCY with or without other immunosuppressive or even myelosuppressive chemotherapy followed by autologous stem cell transplantation has also been used to treat refractory severe autoimmune diseases. Similar to HiCY without stem cell transplantation, durable remissions have been achieved, but most patients eventually relapse within 5 years of therapy. In a report from the European Group for Blood and Marrow

Transplantation, they reported 9 patients of 900 total from 1996-2007 who received a second autologous transplant for SADS. [18] Outcomes were not provided. More recently in a report from the United Kingdom of 70 transplants for SADS from 1997-2009, one patient had an allogeneic transplant three years after an autologous transplant [19].

The decision about when to initiate a second cycle of HiCY is complex and involves careful discussion between the patient and physician, and may also depend upon the quality and duration of response, as well as other potentially available therapies. In our series the discussion was initiated by the patients in all cases, and was likely attributable to the fact that six of the eight patients were refractory to standard therapy, and had few or no good treatment options available. Moreover, all of these six achieved a complete remission after HiCY and were able to taper or discontinue their immunosuppressive medication required to control their disease. Based on these data, we believe that repeat treatment with HiCY should be considered in patients with refractory severe autoimmune disorders who have achieved a high quality remission that has lasted at least 2 years. The possibility that maintenance immunosuppressive therapy, after HiCY re-treatment, may prolong the beneficial effect needs to be tested in a prospective trial.

## Acknowledgements

We are grateful to Dr. Jeffrey Ralph for follow up information on patient F.

**Address correspondence to:** Dr. Amy E DeZern, The Bunting and Blaustein Cancer Research Building I, 1650 Orleans Street, Room 3M87, Baltimore, MD 21287, USA. Phone: 410-5027208; Fax: 410-9558202; E-mail: adezern1@jhmi.edu

## Reference

[1] Brodsky RA, Sensenbrenner LL, Jones RJ. Complete remission in acquired severe aplastic anemia following high-dose cyclophosphamide. Blood 1996; 87: 491-494.

[2] Brodsky RA, Chen AR, Dorr D, Fuchs EJ, Huff CA, Luznik L, Smith BD, Matsui WH, Goodman SN, Ambinder RF, Jones RJ. High-dose cyclophosphamide for severe aplastic anemia: long-term follow-up. Blood 2010; 115: 2136-2141.

[3] Drachman DB, Adams RN, Hu R, Jones RJ, Brodsky RA. Rebooting the immune system with high-dose cyclophosphamide for treatment of refractory myasthenia gravis. Ann N Y Acad Sci 2008; 1132: 305-314.

[4] Krishnan C, Kaplin AI, Brodsky RA, Drachman DB, Jones RJ, Pham DL, Richert ND, Pardo CA, Yousem DM, Hammond E, Quigg M, Trecker C, McArthur JC, Nath A, Greenberg BM, Calabresi PA, Kerr DA. Reduction of disease activity and disability with high-dose cyclophosphamide in patients with aggressive multiple sclerosis. Arch Neurol 2008; 65: 1044-1051.

[5] Tehlirian CV, Hummers LK, White B, Brodsky RA, Wigley FM. High-dose cyclophosphamide without stem cell rescue in scleroderma. Ann Rheum Dis 2008; 67: 775-781.

[6] Petri M, Brodsky RA, Jones RJ, Gladstone D, Fillius M, Magder LS. High-dose cyclophosphamide versus monthly intravenous cyclophosphamide for systemic lupus erythematosus: a prospective randomized trial. Arthritis Rheum 2010; 62: 1487-1493.

[7] Moyo VM, Smith D, Brodsky I, Crilley P, Jones RJ, Brodsky RA. High-dose cyclophosphamide for refractory autoimmune hemolytic anemia. Blood 2002; 100: 704-706.

[8] Brodsky RA, Petri M, Smith BD, Seifter EJ, Spivak JL, Styler M, Dang CV, Brodsky I, Jones RJ. Immunoablative High-Dose Cyclophosphamide Without Stem Cell Rescue for Refractory Severe Autoimmune Disease. Ann Intern Med 1998; 129: 1031-1035.

[9] Dezern AE, Petri M, Drachman DB, Kerr D, Hammond ER, Kowalski J, Tsai HL, Loeb DM, Anhalt G, Wigley F, Jones RJ, Brodsky RA. High-dose cyclophosphamide without stem cell rescue in 207 patients with aplastic anemia and other autoimmune diseases. Medicine (Baltimore) 2011; 90: 89-98.

[10] Emadi A, Jones RJ, Brodsky RA. Cyclophosphamide and cancer: golden anniversary. Nat Rev Clin Oncol 2009; 6: 638-647.

[11] Sladek NE, Kollander R, Sreerama L, Kiang DT. Cellular levels of aldehyde dehydrogenases (ALDH1A1 and ALDH3A1) as predictors of therapeutic responses to cyclophosphamide-based chemotherapy of breast cancer: a retrospective study. Rational individualization of oxazaphosphorine-based cancer chemotherapeutic regimens. Cancer Chemother Pharmacol 2002; 49: 309-321.

[12] Jones RJ, Barber JP, Vala MS, Collector MI, Kaufmann SH, Ludeman SM, Colvin OM, Hilton J. Assessment of aldehyde dehydrogenase in viable cells. Blood 1995; 85: 2742-2746.

[13] Brannagan TH III, Pradhan A, Heiman-Patterson T, Winkelman AC, Styler MJ, Topolsky DL, Crilley PA, Schwartzman RJ, Brodsky I, Gladstone DE. High-dose cyclophosphamide with-

out stem-cell rescue for refractory CIDP. Neurology 2002; 58: 1856-1858.
[14] Gladstone DE, Brannagan TH III, Schwartzman RJ, Prestrud AA, Brodsky I. High dose cyclophosphamide for severe refractory myasthenia gravis. J Neurol Neurosurg Psychiatry 2004; 75: 789-791.
[15] Cutter GR, Baier ML, Rudick RA, Cookfair DL, Fischer JS, Petkau J , Syndulko K, Weinshenker BG, Antel JP, Confavreux C, Ellison GW, Lublin F, Miller AE, Rao SM, Reingold S, Thompson A, Willoughby E. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999; 122: 871-882.
[16] Jaretzki A III, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, Sanders DB. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology 2000; 55: 16-23.
[17] Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer 1996; 32A: 1135-1141.
[18] Farge D, Labopin M, Tyndall A, Fassas A, Mancardi GL, Van LJ, Ouyang J, Kozak T, Moore J, Kötter I, Chesnel V, Marmont A, Gratwohl A, Saccardi R. Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases. Haematologica 2010; 95: 284-292.
[19] Snowden JA, Pearce RM, Lee J, Kirkland K, Gilleece M, Veys P, Clark RE, Kazmi M, Abinun M, Jackson GH, Mackinnon S, Russell NH, Cook G; BSBMT Clinical Trials Committee. Haematopoietic stem cell transplantation (HSCT) in severe autoimmune diseases: analysis of UK outcomes from the British Society of Blood and Marrow Transplantation (BSBMT) data registry 1997-2009. Br J Haematol 2012; 157: 742-746.