

Pemphigus vulgaris treated with allogeneic hematopoietic stem cell transplantation following non-myeloablative conditioning

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Abstract. – Objectives: Successful treatment of severe, refractory Pemphigus vulgaris (PV) is reported.

Methods: Reduced intensity, non-myeloablative conditioning was employed, followed by allogeneic hematopoietic stem cell transplantation (HSCT) from a fully matched sibling.

Results: Treatment of refractory PV with myeloablation and subsequent allogeneic HSCT has been previously reported, and sustained remission with this approach has been achieved. Toxicity, however, related to condition regimens remains high.

Conclusion: Since no cytotoxic chemotherapy was used, it is hereby hypothesized that clinical improvement may result from regulatory action from the donor's marrow: a "graft modifying the disease" effect, which may prove useful in the management of autoimmune diseases.

Key Words:

Pemphigus, Hematopoietic stem cell transplantation, HSCT, Autoimmune diseases.

Introduction

Pemphigus vulgaris (PV) is an autoimmune disease characterized by widespread blistering and denudation of skin and mucosal surfaces. Mortality rates from PV in the era before glucocorticosteroids ranged from 60 to 90%. The defining pathologic feature of PV is the production of circulating IgG that binds to the cell surface of stratified squamous epithelium. Acantholysis with immunoglobulin deposition with or without complement components is the hallmark

of PV¹⁻³. Neonatal PV with spontaneous resolution of the disease in early infancy shows that maternal PV IgG can cross the placenta to cause the disease. PV can be reproduced in mice by passive transfer of IgG from patients with PV.⁴ Intravenous immunoglobulin infusion and plasmapheresis have both been effective in controlling PV, presumably by blocking/eliminating IgG. These observations demonstrate convincingly the central role of PV-causing IgG. Interestingly, production of such IgG exhibits clonal limitation: elimination of certain lymphocyte lines can lead to control of the disease: remission or at least its significant modification, as is evidenced in one patient who received immunoablative (but not myeloablative) high-dose cyclophosphamide without stem cell rescue.⁵ This patient experienced a long-term remission which was later followed by relapse of PV in a much milder form. As no hematopoietic stem cell transplant took place, it appears that, in this case, regulatory T cell action by surviving lymphocyte progenitors and their progeny was able to suppress and later, to regulate the production of PV-causing IgG. With this precedent, hematopoietic stem cell transplantation (HSCT) following non-myeloablative conditioning was considered, for its less toxic profile and for its potential to suppress/regulate PV lymphoid clones.

Case

A 34 year old Caucasian woman presented to one of the Authors (MKT) with a one year history of rapidly expanding flaccid bullae, painful skin erosions and oral ulcers. Lesions were progressively worsening and by the time of her presentation 30% of her skin was affected and nar-

cotics were being used. There was a history of multiple admissions to hospitals for treatment of infections, bacteremia and management of skin lesions. At presentation she was on 80 mg of prednisone per day and oral cephalexin. Tapering of steroids had been attempted several times with immediate flare-ups, but a regimen of 60 mg prednisone every other day had been tolerated for significant lengths of time. Steroid-related toxicity at that point in time already comprised Cushingoid facies, acne, central obesity, striae and muscle wasting. On examination flaccid bullae were present, along with areas of varying hyperpigmentation. Nikolsky sign was positive. Buccal involvement was marked with multiple painful ulcers. Biopsies revealed characteristic suprabasal acantholysis, blisters with keratinocytes in them and dense perivascular lymphocytic/monocytic infiltrates¹. Direct immunofluorescence showed homogeneous staining of intercellular spaces for IgG and complement C3^{1,6-8}. Diagnosis was confirmed with auto-antibodies against desmoglein 1 (160 kd transmembrane glycoprotein) and plakoglobin (85 kd desmosomal glycoprotein)^{3,9,10}. An attempt was made to wean her from steroids by using methotrexate up to a dose of 20 mg twice a week but results were mediocre and relapses frequent. Following consultation (AST) azathioprine was introduced at 1 mg/kg/day which allowed gradual tapering of prednisone to 10 mg every other day over a three month period. Steroids, however, were only discontinued with further increases of azathioprine to a maximum of 3 mg/kg. Subsequent relapses were successfully treated with addition of dapsone first (150 mg per day) and chlorambucil later. Chlorambucil was initiated at 2 mg twice a day (0.05 mg/kg) and gradually increased to 18 mg per day (0.22 mg/kg). Treatment with chlorambucil was limited to six weeks. Upon discontinuation of chlorambucil management continued with azathioprine on a regular basis. Prednisone every other day, dapsone and chlorambucil were all re-introduced later for relapses. Three years after her presentation, the patient was admitted to the hospital with fever, leukocytosis, iron-deficient anaemia, bacteremia and massive elevation of her liver transaminases. Upon her discharge azathioprine was discontinued and a combination of prednisone, dapsone and low dose cyclosporine was used which hardly controlled her PV. By that time the patient had grown depressed and suicidal thoughts were being brought up. Dependence

on narcotics was becoming a significant component of her course. With the precedent of the excellent outcome of autologous HSCT in another autoimmune bullous skin disease published recently, HSCT was offered.¹¹ Considering the risk for relapse following autologous HSCT and the chemotherapy-associated toxicity which was to be imposed on a patient who had already suffered the significant toxic effects of a multitude of immunosuppressants, non-myeloablative, reduced intensity conditioning was chosen which was to be followed by allogeneic HSCT.

Methods

The patient's sister molecular HLA typing yielded a full match (6/6). Following six days of granulocyte colony stimulating factor (G-CSF) at 15 µg/kg and leukapheresis, 100×10⁶ CD34+ cells per kg of recipient's weight were obtained from the donor. The conditioning regimen for the recipient included alemtuzumab (Campath), total of 1 mg/kg, given in gradually increasing doses on days -7 to -3 before transplantation. On day -2 before transplantation a single dose of 300 cGy of total body irradiation was administered. Oral sirolimus was started one day after the transplantation. Standard supportive care was provided which included penicillin V potassium 250 mg twice a day and pneumococcal vaccination. Engraftment was assessed by means of short tandem repeats polymorphisms¹².

Results

The conditioning regimen was tolerated. Twenty two million CD34+ cells per kg of body weight were administered. Neutropenia (neutrophil count less than 0.5×10⁹/liter) developed on day +9 after transplantation and persisted through day +22, the nadir having been 0.25×10⁹/liter on day +14. Febrile neutropenia with negative blood cultures developed twice following the procedure and was treated with intravenous vancomycin and oral ciprofloxacin. Lymphopenia (lymphocyte count less than 0.75×10⁹/liter) persisted for 6 months and thrombocytopenia (count less than 50×10⁹/liter) for 9 days.

At 18 months the percentage of circulating donor myeloid cells was 79% while donor T cells were 55%. Steroids, cyclosporine and dapsone have all been discontinued. Treatment with sirolimus continues. Graft versus host disease did not develop. The only significant adverse events were arthralgia affecting mostly ankles, knees and wrists and arthritis of both ankles. Symptoms were severe enough to interfere significantly with daily activities but eventually their severity declined by the ninth month after transplantation following reduction in the sirolimus dosing. At 24 months post transplantation the patient remains disease-free.

Discussion

Given the pathology of PV, allogeneic HSCT following myeloablation is a sensible approach to refractory PV, which however is hampered by the high toxicity of conditioning. Myeloablative procedures with subsequent autologous HSCT has been tried with success in bullous autoimmune skin disease but again treatment-associated toxicity remains considerable¹¹. Furthermore, autologous HSCT not only does not eradicate autoimmune lymphoid clones but is also likely to re-introduce autoimmune active lymphocytes¹¹. Reduced intensity non-myeloablative conditioning protocols for HSCT have their limitations too: they have been used successfully in the treatment of hemoglobinopathies and enzyme deficiencies where stem cells are expected to provide the missing protein, but experience with autoimmune diseases is so far scarce¹³. Reluctance to use reduced intensity HSCT in autoimmune diseases results from well deserved skepticism: a mixed chimeric state with preservation of the recipient's own bone marrow does not eliminate lymphoid clones originally responsive for the autoimmune process. In spite of limited experience with reduced intensity non-myeloablative HSCT, we were encouraged to proceed because of previously reported favorable response of PV to doses of cyclophosphamide high enough to result in immunoablation but not sufficient to cause aplasia⁵. The Authors of this study raised the issue of differential response of marrow cell lines to high doses of cyclophosphamide. More importantly, beyond the practical value of their observation which, in their case, alleviated the need for stem cell rescue and

transplantation, their experience indicated that PV is the result of mono/oligo-clonal activation and proliferation of auto-reactive lymphoid series⁵. If this is the case mixed chimerism may significantly modify PV if it does not eradicate it. Based on this hypothesis non-myeloablative HSCT was attempted in our patient. This case demonstrates that regulation and possibly suppression of the involved clones is possible by means of HSCT leading to a mixed chimeric state. This is an entirely new application for non-myeloablative HSCT. Of course, the use of sirolimus, an agent with proven T-regulatory properties and a marked anti-proliferative effect on T-cells is not only operative in preventing graft versus host disease, but is also conducive in developing a highly regulatory cytokine environment which, in its turn, independently suppresses PV activity^{14,15}. The use of non-myeloablative allogeneic HSCT along with subsequent administration of sirolimus may become a new therapeutic modality in the treatment of autoimmune diseases, which may be understood as a "graft-modifying-the-disease" effect.

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