Bone Marrow Transplantation (2004) 34, 1097–1098

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High-dose immune suppression and autologous hematopoietic stem cell transplantation in refractory pemphigus foliaceus

Bone Marrow Transplantation (2004) **34,** 1097–1098. doi:10.1038/sj.bmt.1704679
Published online 18 October 2004

Although autologous hematopoietic stem cell transplantation (HSCT) has been used as treatment for numerous autoimmune diseases,[1–3] bullous autoimmune disorders have not, to our knowledge, been treated by HSCT. Pemphigus foliaceus (PF) is an autoimmune disease with antibody titers against desmoglein-1 (Dsg-1)[4] that correlate with the extent and activity of disease. Treatment refractory cases of PF occur and the cause of death is generally infection.

We report a patient treated under an Institutional Review Board and the United States Food and Drug Administration approved protocol for refractory bullous skin diseases that include PF, pemphigus vulgaris (PV), and cicatricial pemphigoid (CP). Patients on this protocol must have failed to respond to prednisone 0.5 mg/kg/day for more than 3 months and at least two other immunosuppressive agents that include cyclophosphamide (CY), mycophenolate mofetil (MMF), gold, cyclosporine, methotrexate (MTX), or plasmapheresis. Failure is defined as the involvement of more than 10% of body surface area, mucosal lesions or recurrent infections requiring hospitalizations.

PBSC are mobilized with CY 2 g/m^2 i.v. and G-CSF 10 mcg/kg/day s.q. beginning 72 h after completion of CY administration. CD34$^+$ enrichment was performed using an Isolex 300i® cell separator (Baxter, Chicago, IL, USA). The high-dose immune-suppressive regimen consisted of CY 50 mg/kg/day i.v. for 4 days (days −5, −4, −3, and −2, total 200 mg/kg), and rabbit antithymocyte globulin (rATG) 0.5 mg/kg/day i.v. on day –6 and 1.25 mg/kg/day i.v. on days −5, −4, −3, and –2 (total 5.5 mg/kg). Mesna was administered along with CY. Methylprednisolone 1.0 g/day was administered prior to each dose of rATG. G-CSF s.q. (5 mcg/kg/day) was started on day 0 until the ANC reached 500/mcl. Peri-HSCT prophylactic antibiotics included oral ciprofloxacin, intravenous vancomycin, valacyclovir, fluconazole, and pentamidine nebulizer. Post-HSCT prophylactic antibiotics included fluconazole and trimethoprim/sulfamethoxazole for 6 months and valacyclovir for 12 months.

The patient, a 31-year-old Hispanic female, had erythematous desquamating annular plaques with an erythematous rim, peripheral scale and vesicles diffusely on her head, trunk, and extremities. Punch biopsy revealed findings consistent with PF. Pemphigus antibody titer was 1:640 by serum indirect immunofluorescence. ELISA was positive for reaction with desmoglein-1. Prior treatments included topical betamethasone, oral prednisone, azathioprine, MMF, dapsone, and finally oral CY at 75 mg/day for 9 months without effect. Since diagnosis, prednisone was never less than at 10 mg/day with frequent dose escalation depending on disease activity. Pre-transplant, she had diffuse active skin lesions covering 20% of her body surface area (Figure 1).

HSCT was well tolerated. The duration of ANC less than 500/mcl was 7 days. Culture-negative neutropenic fever was present for 1 day. Other transplant toxicities were grade I (by NCI toxicity criteria) nausea and grade II anorexia. Otherwise, the transplantation course was without unexpected toxicity. No early or late opportunistic infections have occurred.

Following HSCT, skin lesions gradually disappeared over 2 months and prednisone was tapered off within 4 months. Serum autoantibody titer gradually decreased from 1:640 pre-transplant to 1:160 at 6 months and 1:20 at 12 months post-transplant, respectively. A complete cutaneous remission was maintained until 10 months following HSCT, when a few small foci of erythematous plaques occurred on the nose and scalp. Punch biopsy of a lesion revealed the recurrence of PF that responded to intermittent topical corticosteroids alone. No other lesions have occurred and no systemic therapy has been required for 19 months following HSCT. Figure 2 was taken 15 months post transplant. Her Karnofsky performance status remains 100%.

Cutaneous autoimmune bullous disorders represent an array of distinct skin diseases including PV, PF, paraneoplastic pemphigus, bullous pemphigoid, CP, pemphigoid gestationis, dermatitis herpetiformis, linear IgA disease and epidermolysis bullosa acquisita, among others. Many of these disorders have known autoreactive antibodies. The hallmark of PF is IgG autoantibodies directed against desmoglein 1, a 160 kDa transmembrane glycoprotein that is expressed on the cell surface of keratinocytes.[4] As the autoantibodies in PF and PV are pathogenic and play a primary role in blister formation, a direct correlation exists between disease activity and antibody titer.[5] Patients with PF present clinically with superficial, fragile vesicles that rupture to form well-demarcated, scaly, crusted erosions on an erythematous base.

In patients with widespread disease, systemic corticosteroids are first-line therapy and result in rapid remissions in the majority of patients.[6] However, the significant morbidity associated with prolonged systemic corticosteroids limits their utility. Commonly utilized steroid-sparing agents include azathioprine, CY, gold salts, cyclosporine, MTX, MMF, dapsone, tetracycline and minocycline. Although most cases can be controlled with conventional therapies, severe cases may be refractory and a breakthrough therapy is needed.

While there are no prior reports of HSCT for bullous skin diseases, Nousari *et al* have reported cases of pemphigus treated with high-dose CY without stem cell transplant.[7–9] To our knowledge, this is the first report of autologous HSCT transplantation for autoimmune bullous skin diseases. Whether our regimen using high-dose CY

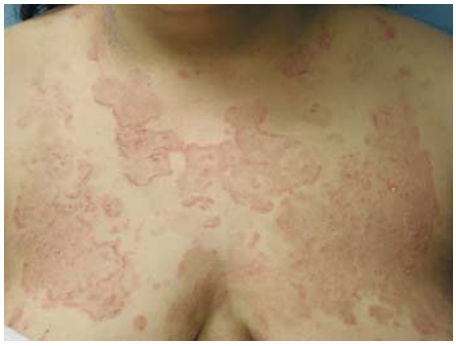

Figure 1 Skin before HSCT.

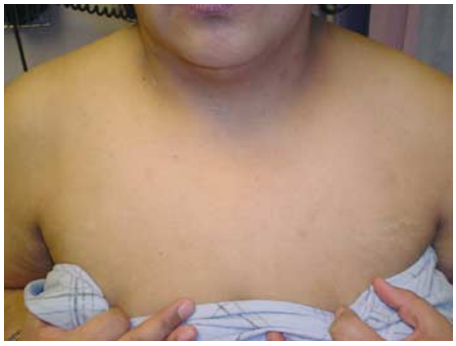

Figure 2 Skin 15 months after HSCT.

and rATG with CD34 selected PBSC is superior to the regimen using high-dose CY without stem cells is currently unknown. Our patient responded dramatically with a drug-free remission. While a very limited relapse (<1% body surface area involved) occurred at 10 months post HSCT, it was transient. Re-induction of clinical remission readily occurred to only topical corticosteroid therapy. Although longer observation and more patients are necessary, our result suggests that further studies of HSCT in refractory autoimmune bullous skin disorders appear warranted.

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