Correspondence

Federico Silvestri, M.D., Division of Hematology, University Hospital, p.le S. Maria della Misericordia, 33100 Udine, Italy. Phone: international +39-0432-559662 – Fax: international +39-0432-559661 – E-mail: ematologia@drmmm.uniud.it

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Effectiveness of extracorporeal photochemotherapy in treating long-term refractory chronic graft-versus-host disease

We report two cases of severe refractory progressive chronic graft-versus-host disease (cGvHD) which improved dramatically after extracorporeal photochemotherapy. This procedure, based on functional changes of lymphocytes induced by 8-methoxypsoralen and UVA administered to leukapheresis collections, could be a useful treatment for cGvHD, even after many years of unsuccessful immunosuppressive approaches.

Sir,

About 25% of pediatric recipients of allogeneic marrow transplantation develop chronic graft-versus-host disease (cGvHD), which may be limited or extensive with multiorgan involvement, especially of the skin, mouth, gut, liver and eyes.[1] Since 1990 some authors have reported that refractory cGvHD, besides benefitting from standard immunosuppression, can also benefit from extracorporeal photochemotherapy (ECP), which consists of sensitization of peripheral leukocytes by 8-methoxy-psoralen (8-MOP) and extracorporeal exposure of leukeapheresis collections to UVA.[1-4]

We describe two pediatric patients successfully treated with ECP for severe persistent cGvHD after many years of ineffective immunosuppression.

Case #1. A 14-year old girl transplanted for acute lymphoblastic leukemia from her HLA-identical brother in 1988, developed progressive refractory cGvHD, which subsequently involved the skin (lichen-planus-like papulae, scleroderma, diffuse alopecia), mucosa (oral sicca-syndrome), gut (dysphagia, diarrhea, weight loss), musculoskeletal system (contractures, arthritis), lungs (obstructive respiratory impairment), and immuno-hematopoietic system (pancytopenia, positivity for autoantibodies, recurrent respiratory infections), with a Lansky performance score lower than 70%. For eight years steroids, cyclosporin-A, azathioprine, thalidomide (Grunenthal GmbH, Stolberg Rhld, Germany), methotrexate, lymphoid irradiation and PUVA courses were used in various combinations. Since the cGvHD did not resolve and severe side-effects (hypertension, insulin-dependent diabetes, cataracts, peripheral polyneuropathy) developed, in May 1996 ECP treatment was started. At that time, the patient's C-reactive protein (CRP) concentration was 48 mg/L, anti-nuclear (ANA) and anti-DNA antibodies were strongly positive, and complement fraction 3 and 4 (C3 and C4) levels were 65 and 14 mg/dL, respectively. Improvements were seen after three ECP procedures, which were continued without side-effects for a total of 21 procedures,[3] by which time the skin lesions had markedly improved, joint contractures had almost completely resolved, arthritis had disappeared, respiratory function tests had almost normalized, upper respiratory infections occurred very rarely and daily insulin requirement was lower. The Lansky performance score increased to 90%. CRP, C3, and C4 levels returned to normal values, anti-DNA antibodies became negative, whilst ANA remained positive. Immunosuppression was progressively tapered down and discontinued in June 1998 without reacutization of the GvHD.

Case #2. A 5-year old boy, transplanted in 1992 for Fanconi's anemia from his HLA-identical brother, developed progressive extensive cGvHD, barely controlled by standard immunosuppression, which flared again in the oral mucosa six years after the transplantation, despite steroid treatment being resumed in combination with thalidomide and azathioprine. In July 1998 ECP was started and improvements were noticed after three ECP procedures, which were continued without side-effects for a total of 12 procedures. The Lansky performance score increased to 90% and oral lesions almost completely disappeared. Steroid treatment was progressively tapered down and then discontinued. The planned schedule was interrupted because of poor venous access and, a few months after, cGvHD flared up again and conventional treatment was resumed.

Leukaphereses were performed by means of a continuous flow cell separator using peripheral venous access; at least two blood volumes were processed;

mean volumes of 140 mL, containing 3.8×10^9 cells were collected per procedure, with the percentage of mononuclear cells ranging from 76 to 92%. Normal saline was added to the collection bag to make a volume of 300 mL, and the final hematocrit was <2% (median: 1.3%). The yielded buffy coat was transferred into a thin plastic bag and then 8-MOP was added to a final concentration of 200 ng/mL; finally, the product was exposed to UVA irradiation (365 nm,2 J/cm^2) and then reinfused into the patient. The schedules described by Rabitsch (two consecutive days every other week for two months, then two consecutive days monthly)[3] and Besnier (twice weekly for 3 weeks, once weekly for 2 weeks and then every other week)[4] were adopted for the first and second patient respectively.

Most data report that ECP is beneficial when adopted early after bone marrow transplantation;[5-10] our experience confirms that ECP is recommendable even after many years of refractory cGvHD, and that good venous access is crucial in order to complete the schedule.

Ettore Biagi,° Paolo Perseghin, Filippo Buscemi,* Maria Dassi,* Attilio Rovelli,° Adriana Balduzzi°*

*°Clinica Pediatrica dell'Università di Milano - Bicocca; *Servizio Trasfusionale, Unità di Aferesi, Ospedale S.Gerardo, Monza, Italy*

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Correspondence

Adriana Balduzzi, M.D., Clinica Pediatrica dell'Università di Milano, Ospedale San Gerardo, via Donizetti 106, 20052 Monza (MI), Italy. Phone: international +39-039-2333513 – Fax: international +39-039-2301646 – E-mail: ctmomonza@libero.it

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Delayed graft-versus-leukemia effect after allogeneic peripheral stem cell transplantation in a patient with chronic lymphocytic leukemia

We provide evidence of a graft-versus-leukemia (GvL) effect in a highly refractory B-chronic lymphocytic leukemia (B-CLL) treated with allo-peripheral blood stem cell transplantation (allo-PBSCT) in which a complete response was achieved coinciding with the development of acute graft-versus-host disease (GvHD). However, the patient died after extensive chronic GvHD. Allo-PBSCT is effective in generating GvL but chronic GvHD must be controlled.

Sir,

A 45-year old man was diagnosed as having B-CLL stage B (multiple lymphadenopathy and hepatosplenomegaly). His white blood cell count was 303×10^9/L (87% lymphocytes), hemoglobin 11.3 g/dL and platelets 172 $\times10^9$/L. A blood smear revealed typical CLL morphology. Bone marrow and lymph node biopsies showed a diffuse pattern of infiltration. Flow cytometry analysis was compatible with the diagnosis and monoclonal IgH rearrangement was found (Figure 1). Computed tomography of thorax, abdomen and pelvis revealed multiple lymphadenopathy on both sides of diaphragm.

The patient received two lines of chemotherapy (mitoxanthrone/fludarabine and hyperCVAD) without response.[1] Salvage chemotherapy (ESHAP)[2] was administered producing a partial response in lymphadenopathy and a significant decrease in peripheral lymphocytes (8.3×10^9/L). However, a 77% bone marrow infiltration persisted. As the patient had an HLA-identical sibling donor, an allo-PBSCT was performed. Cyclophosphamide and total body irradiation were used as the conditioning regimen. G-CSF mobilized PBSC: 3.29×10^6/kg CD34$^+$ and 3.56×10^8/kg CD3$^+$ cells. GvHD prophylaxis consisted of cyclosporin-A (CsA) and methylprednisolone.

Neutrophil ($\geq0.5\times10^9$/L) and platelet ($\geq20\times10^9$/L) engraftment was obtained on days +16 and +15, respectively. During the first month, a reduction in the number of lymphocytes was observed, with a mini-