



The role of photopheresis in the treatment of graft-versus-host disease

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KEY WORDS

Hematopoietic stem-cell transplantation, graft-versus-host disease, GVHD, acute GVHD, chronic GVHD, T-regulatory cells, immunomodulatory therapy, photosensitizing agent, anti-inflammatory cytokines, pro-inflammatory cytokines, photopheresis, Total Skin Score, targeted symptom assessment

INTRODUCTION

Hematopoietic stem-cell transplantation using cells obtained from peripheral blood, bone marrow, or cord blood is being used to treat not only genetic and immunologic diseases, but also a variety of hematologic malignancies. Significant advances have been made in the management of such procedures, leading to improved rates of engraftment, prognosis, and quality of life, but graft-versus-host disease (GVHD) continues to be a major problem¹.

Traditionally, GVHD has been divided into an acute syndrome that occurs within 100 days of transplant and a chronic disease that occurs after that time. This classification was quite arbitrary and, actually, quite unsatisfactory—a problem that led to an National Institutes of Health (NIH) consensus conference that devised a new classification². The classification now includes two subcategories in acute GVHD (aGVHD), namely, classical aGVHD and persistent (or “late-onset”) aGVHD. Chronic GVHD (cGVHD) is now classified as classical cGVHD and overlap syndrome. A clinical scoring system with four categories was also devised for each organ system: 0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms. Guide-

lines for global assessment of cGVHD severity were also proposed.

The incidence and severity of aGVHD depends in good measure on the degree of mismatch between the donor and the host histocompatibility antigens. Acute GVHD occurs when immunocompetent donor T cells are transplanted into an immunocompetent host whose histocompatibility antigens are different. Its occurrence ranges from 30%–50% in patients who receive stem cells from a histocompatibility-matched related donor, but it increases to 50%–80% in patients who receive cells from a histocompatibility-matched unrelated donor in spite of immunoprophylaxis and T-cell depletion. Mortality can range up to 50%³.

Chronic GVHD occurs in 30%–60% of patients who receive an allogeneic stem cell graft. It affects a wider range of organs than does aGVHD. It is the most troublesome complication of hematopoietic stem-cell transplantation, often presenting as a systemic disorder exhibiting features of such autoimmune diseases as scleroderma, sicca, and systemic lupus erythematosus. Organs commonly involved include eye, liver, lung, and gastrointestinal tract. From experimental studies, a number of theories regarding the pathogenesis of cGVHD have been developed⁴:

- Thymic damage and defective negative selection of T cells generated from marrow progenitors after hematopoietic cell transplants
- Aberrant production of transforming growth factor β
- Autoantibody production
- Deficiency in number or function of T-regulatory cells

Thus, it is conceivable that, in humans, multiple pathophysiologic mechanisms are at play to produce cGVHD.

Corticosteroids are the mainstay of treatment for cGVHD. Unfortunately, these agents are not always effective, and their use may lead to devastating complications. Additional agents are therefore used, including methotrexate, calcineurin inhibitors, sirolimus, mycophenolate mofetil, pentostatin,

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photopheresis, daclizumab, and anti-tumour necrosis factor (TNF) drugs.

EXTRACORPOREAL PHOTOPHERESIS

Extracorporeal photopheresis (ECP) is a cell-based immunomodulatory therapy that involves collecting leukocytes from peripheral blood. These cells are exposed to a photosensitizing agent, 8-methoxypsoralen, and are then treated with ultraviolet (UV) radiation, after which they are re-infused. This procedure, which results in crosslinking of pyrimidine bases in DNA, produces massive apoptosis of the treated cells. The procedure was developed in 1987 by Dr. Richard Edelson for use in treating cutaneous T-cell lymphoma⁵.

The mechanism of action of ECP has been extensively explored, and several theories have been advanced:

- Clearance of apoptotic cells by antigen-presenting cells results in differentiation of those cells into a more tolerogenic phenotype^{6,7}, leading to decreased stimulation of effector T cells or their deletion.
- Production of anti-inflammatory cytokines, especially interleukin 10, is increased^{8,9}.
- Production of pro-inflammatory cytokines, especially interleukin 12 and TNF α , is decreased¹⁰.
- Generation of CD4+, CD25+, GITR+, Foxp3+, CD62L+ T-regulatory cells occurs^{9,11,12}.

It is of considerable interest that the T- and B-cell responses to novel and recall antigens remain intact in patients treated with ECP¹³. Thus, there appears to be a reduced risk of infections with the use of ECP as compared with the use of other immunosuppressive agents^{13,14}.

Equipment

The equipment for photopheresis was developed by Therakos, a Johnson and Johnson company (Raritan, NJ, U.S.A.), based on Latham bowl technology. Much of reported use of photopheresis has involved a second-generation model—namely, the Therakos Uvar XTS system. This discontinuous, but completely contained, automated procedure collects some 5%–8% of circulating white blood cells into a plastic bag. A UV photosensitizing agent, 8-methoxypsoralen, is added to the bag, and the treated cells are then subjected to 1.5 J UVA light. Afterwards, the cells are re-infused.

The difficulty with this technology is its discontinuity. To collect the leukocytes, the bowl first has to fill with red blood cells. There are two bowl sizes: 125 mL and 225 mL. If the patient's hematocrit is low, the volume of blood needed to fill the bowl with red blood cells may be very large. It is recommended that the extracorporeal volume not exceed the total blood volume by more than 15%. Thus, the smallest patient

recommended for treatment by this method is someone 35 kg in weight with a hematocrit of at least 19%.

A third-generation apparatus has now been introduced by Therakos. The Therakos Cellex still uses the Latham bowl technology, but its single- or double-needle continuous-flow system is completely automated. The tubing volume for the single-needle procedure is 260 mL; for the double-needle procedure, it is 216 mL. The average treatment time for a patient was 180 minutes using the Therakos Uvar XTS. With the new apparatus, a single-needle procedure takes 100 minutes, and a dual-needle system, only 75 minutes.

In France and Italy, photopheresis is carried out using different equipment. The two-step procedure in those countries involves collecting the leukocytes with the Cobe Spectra separator [CaridianBCT (Canada), Mississauga, ON]. The collected mononuclear cells are then treated with a 8-methoxypsoralen and the buffy coat is transferred to a special UVA-permeable bag made by Macopharma (Tourcoing, France). The UV radiation is performed by an Uvamatic Irradiator (Vilber Lourmat, Marne-La-Vallée, France) at 2 J/cm³, after which the cells are re-infused. This procedure can therefore be used on children weighing as little as 13 kg¹⁵.

Safety

More than 500,000 ECP treatments have been performed worldwide. The incidence of reported side effects is extremely low at less than 0.003%. Significantly, the incidence of infections related to the procedure in this patient population is very, very low. Many of the complications are related to vascular access. It would be preferable to use peripheral veins, but patients with cGVHD frequently have poor veins, and alternative access must therefore be used. When central venous catheters are used, complications such as infection, clotting in the catheters, deep venous thrombosis, and vessel stenosis can occur. Another option is the use of Vortex ports (Rita Medical Systems, Manchester, GA, U.S.A.) or Cathlink 20 ports (Bard Access Systems, Salt Lake City, UT, U.S.A.)¹⁶. These systems are entirely underneath the skin. They are especially useful in children, in whom hygiene may be a problem. The safety of the new Therakos Cellex photopheresis system in cutaneous T-cell lymphoma has also been reported¹⁷.

EVALUATION OF ECP THERAPY OF GVHD

In large measure, the results of ECP consist of observational data from case reports and from small, uncontrolled series. Evaluation has been difficult because GVHD affects many organ systems, because the cutaneous manifestations are protean¹⁸, and because in nearly all cases, ECP has been used in conjunction with other treatment modalities—most frequently as a steroid-sparing maneuver or as a last

resort in difficult cases. The lack of suitable criteria for assessing therapy has been addressed by an NIH consensus conference² that established a redefinition of GVHD and a standard for lesions in various organs. Criteria to assess therapeutic response have also been developed¹⁹.

Acute GVHD

From case reports and small uncontrolled series, ECP in aGVHD can be seen to have been used almost exclusively in patients in whom conventional immunosuppressive therapy failed. A phase II study by Greinix *et al.*²⁰ involving 38 patients reported complete remission in 86%, 55%, and 30% of patients with grades 2, 3, and 4 aGVHD respectively. The best results were obtained in 82%, 61%, and 61% of patients with skin, liver, and gut aGVHD respectively.

The experience in children is much more limited, but suggests that similar results can be obtained¹⁵. Therakos sponsored a prospective controlled trial of ECP in aGVHD, planning to enrol 30 centres and to recruit about 120 patients per treatment arm. However, the study was stopped because of low patient accrual.

Chronic GVHD

The experience with ECP in cGVHD is more extensive, but also consists mainly of case reports and small uncontrolled series. The protocols are variable, but usually consist of 2 or 3 treatments every 1 or 2 weeks initially^{13,19,20}. Once the regimen starts to show a benefit, the ECP can be tapered to 2 treatments every 3–4 weeks. However, once a treatment is proving to be efficacious, then the usual practice is to start by reducing immunosuppressive agents, especially steroids. If there is no response in 3 or 4 months, then the procedure should be stopped. In sclerodermatous skin changes, the improvement occurs very gradually, and 6–12 months of treatment may be required before tapering is used.

A consensus statement on use of ECP in the treatment of cutaneous T-cell lymphoma and cGVHD has been published by a group from the United Kingdom¹⁴, and recently, two prospective studies on the use of ECP in cGVHD were published. Foss *et al.*²¹ reported on a prospective study of ECP in extensive steroid-resistant cGVHD that enrolled 25 patients. The ECP was administered for 2 consecutive days every 2 weeks in 17 patients and weekly in 8 patients until the best response or stable disease was obtained. The median duration of therapy was 9 months. Improvement in skin or visceral cGVHD (or both) was reported in 71% of the overall cohort and in 61% of high-risk patients.

Flowers *et al.*²² reported on a multicentre prospective phase II randomized study of ECP for the treatment of cGVHD. It was conducted in 23

transplant centres in North and South America, Europe, and Australia. The 95 enrolled patients were randomized either to ECP plus standard therapy or to standard therapy alone. The patients randomized to ECP received 12 weeks of ECP treatments. The schedule was 3 treatments during week 1 and then 2 treatments on consecutive days each week during weeks 2 through 12. Cutaneous disease was assessed by a blinded trained observer using the Total Skin Score, which grades 10 body regions on a scale from 0 to 5 (0 = normal; 1 = discoloured or alopecia; 2 = lichenoid plaques thickened, able to move and pinch; 4 = hidebound, unable to move or pinch; 5 = grades 3 or 4, with overlying erythema; maximum score: 50). Quality of life was measured using the median Targeted Symptom Assessment, which patients were asked to complete at baseline and at variable periods thereafter. This assessment revealed a significant improvement in favour of ECP. The conclusion reached was that ECP had a steroid-sparing effect in the treatment of cGVHD.

FUTURE DIRECTIONS

There is a definite need for randomized controlled trials of various treatments for GVHD^{4,23}. The development of biomarkers of GVHD would assist greatly in evaluating the efficacy of therapies²⁴.

There is considerable evidence in the literature that ECP increases the number of T-regulatory cells. It is therefore interesting that the calcineurin inhibitors commonly used to treat GVHD actually decrease the number of those cells, whereas sirolimus increases their number²⁵. Mycophenolate mofetil does not affect the function of regulatory cells; corticosteroids improve their survival and function²⁵.

In cGVHD patients with severe sclerotic skin changes, the response to ECP can be quite dramatic. A number of immune-mediated mechanisms have been implicated in the production of fibrosis⁴, and the innate immune system plays an integral role in infection and inflammation²⁶. Therefore, it is also intriguing to think that this mechanism of action is another in which ECP might be worthy of examination.

Photopheresis is currently available in Calgary, Montreal, Saskatoon, Toronto, Vancouver, and Winnipeg.

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