[Frontiers in Bioscience 14, 4769-4777, January 1, 2009]

Extracorporeal photoimmunotherapy-photopheresis

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1. ABSTRACT

Extracorporeal photoimmunotherapy-photopheresis (ECP) is an immunomodulatory therapy, which basically consists of separating the patient's leucocyte rich plasma from the red blood cell fraction, followed by extracorporeal administration of a photosensitizer and UVA light prior to reinfusion of the treated cells. Successful use of ECP has been reported in patients with cutaneous T cell lymphoma, the Sezary syndrome variant, graft-versus-host disease, cardiac transplant rejection and other T cell mediated/autoimmune and autoimmune diseases. Apoptosis of malignant lymphocytes and presentation of their antigens to anti-tumor CD8+ T cells with induction of an anticlonotypic response by CD8+ effector cells against the CD4+ neoplastic T cells was one of the intial mechanisms of action proposed. The exact mechanism by which ECP exerts its therapeutic effect remains to be further explored and is still uncertain. The better understanding of its mode of action and the clinical benefits of ECP are important findings that provide additional tools to increase the therapeutic armamentarium in a number of acute and chronic T cell mediated diseases.

2. INTRODUCTION

Extracorporeal photochemotherapy or photopheresis (ECP) was first introduced in 1987 for the management of patients with cutaneous T cell lymphomas (CTCL) (1). Since then, the ECP has been applied as a main therapy for various other T cell mediated diseases in and beyond dermatology, including autoimmune diseases, rejection of solid-organ grafts and inflammatory dermatologic diseases (2-7). Up to the present it remains the only FDA approved tumor targeting selective immunotherapy for the treatment of cancer. Though many studies have been conducted, including animal models and *in vitro* studies, the exact mode of action on a molecular basis still remains unclear. The photopheresis procedure takes place in three steps: leukapheresis, photoactivation, and reinfusion (8-10). During photopheresis, the patients' plasma and leukocyte-rich fractions are separated by centrifugation, then passed through a thin, UV–penetrable plastic plate, followed by exposure to a photosensitizer. At present photosensitization is achieved by either giving 8-methoxypsoralen (8-MOP) to the patient 2 hours prior to the procedure, or by adding a photosensitizing agent directly into the leukocyte-rich fraction (e.g.: UVADEX).

The latter avoids unwanted side effects such as nausea and provides a more consistent drug level within the machine (11). The treated leukocytes are re-infused after a minimum exposure of 1,5 hours. Depending on the underlying disease and various protocols, this treatment is usually repeated on 2 successive days, at 4 week intervals. The total UVA dose delivered has been determined to be 2 J/cm^2. ECP is not inexpensive, somewhat time consuming and approved indications are restricted; side effects are minimal as the experience with this therapy spans over 20 years. In some patients, volume changes due to loading with physiological saline can lead to changes in blood pressure and congestive heart failure when predisposed. Anticoagulation can lead to bleeding complications and some patients complain about prolonged recumbency. Excessive frequency of treatment in some patients has been associated with a decrease in the red blood cell fraction requiring treatment. The photopheresis procedure is available worldwide today in over 150 centers.

3. HISTORY

Over 2 decades ago, Edelson and coworkers published the first encouraging results of the use of ECP in 37 patients with advanced cutaneous T cell lymphomas (CTCL) (1). The clinical thought derived from the observation that in an animal model, after lethally damaging an autoreactive T cell clone and subsequent re-infusion of viable autoreactive T cells, disease was not induced (12, 13). The basic hypothesis was that an induced clone-specific immune reaction might limit the activity of an aberrant population of T cells and could be of therapeutic value in patients with diseases mediated by circulating T cells (1, 8). Also the fact that psoralen-UVA treatment of the skin (PUVA) in these patients contributed to a systemic improvement supported this hypothesis.

The Sezary syndrome, a leukemic form of CTCL with erythroderma with often high numbers of circulating T cells in peripheral blood and an expected 5-year survival rate of 24% (14), supplied the perfect clinical setting. Twenty seven patients (73%) achieved response to treatment and in eleven successfully treated patients with CTCL of known clonal origin, several patterns of persistent T lymphocyte subs*et al*terations were noted. T4 cells decreased and T8 cells increased, leading to a significant decrease in the T4/T8 ratio (8). The accessibility of subsets of leucocytes by ECP offered the perfect setting by which the lymphocytes could be damaged but at the same time retain their antigenicity until they were sequestered by an uninhibited immunologic response. Various studies followed, *in vitro* and *in vivo* studies, either to highlight the mechanism of action or to extend the therapeutic applicability of ECP for a variety of T cell mediated disorders including graft-versus-host disease (GVHD) (2, 15), scleroderma (8), solid organ transplant rejection (16, 17, 18), oral lichen planus (5), autoimmune bullous disorders (19).

4. MECHANISMS OF ACTION

4.1. General aspects

Photopheresis and its mechanism of action have been intensively studied in patients with Sezary syndrome (20). In this cohort of patients, the induction of an immune response against defined lymphocyte populations seems to account for the therapeutic effect. In these patients, complete clinical response has been shown to correlate with the complete disappearance of the malignant T cell clone (20). Even though the precise mechanism underlying the observed efficacy of ECP as a therapy still remains to be elucidated, some hypothetic mechanisms of action have been proposed with regard to the pathogenetic differences of the underlying T cell mediated diseases being treated. An important role is attributed to regulatory T cells (Tregs), which are naturally occurring CD4+CD25+ T cells, and whose main physiological role is to switch off autoreactive T cells, thus maintaining self-tolerance (21). Preliminary data shows that the percentage of circulating, functional Tregs can be increased after ECP (22), even though this increase does not easily translate into clinical improvement of patients with chronic graft versus host disease. Other experimental results implied that ECP can also lead to the maturation of dendritic cells from monocytes, the most efficient antigen presenting cells for induction off anti-tumor immunity (23). The development of clinically relevant anti-tumor response in numerous CTCL patients treated with ECP suggests that these responses are due, at least in part, to the generation of dendritic cells capable of ingesting apoptotic CTCL cells and presentation of their antigens to anti-tumor CD8+ T cells (23). Several studies have tried to identify the exact cells and their contents responsible for the action of ECP, one of them being the induction of lymphocyte apoptosis (2, 24). Following ECP induced apoptosis, normal T lymphocytes are replaced at a greater rate than malignant cells and migrate to the peripheral blood (24). Monocytes that do not become apoptotic, produce increased levels of TNFα, which can augment a number of antitumor immune responses (24). One important finding of numerous studies trying to highlight the immunogenic mechanism effected by ECP, is that it does not appear to suppress specific B cell function nor T cell responses, and therefore not induce a generalized immunosuppression (44). Observations in experimental animal models support the evidence that ECP induces specific immunity against pathogenic T cell clones, without suppressing the cellular nor humoral component of the immune system, thus not increasing, but actually reducing, the incidence of infections or neoplasms (44).

4.2. Specific aspects

4.2.1. Cutaneous T cell lymphomas

After the first therapeutic success in patients with refractory CTCL (1, 8), ECP has been studied in numerous therapeutic trials to assess the optimal indication and increase the therapeutic armamentarium for different stages of CTCL (26, 27, 28). In the management of CTCL, ECP is mainly used for the treatment of erythrodermic patients, including those with Sezary syndrome with a high number of circulating atypical mononuclear cells (Sezary cells). Overall response rates are reported between 31% and 86%, whereas rates for complete remission are much lower, ranging from 0 to 33% (29, 30, 31, 32). Individual clinical, immunological and laboratory entry data of patients and different pre-therapies may relate to the differences in response rates published. Favorable response rates to ECP

have been associated with early intervention, normal to high CD8+ cell counts, discrete number of Sezary cells and sufficient immunologic reserve (33, 34, 26). However, some of these results are inconsistent, similar to studies reporting on survival data of patients with CTCL treated with ECP (35, 36). Median survival is dependent on the extent of disease, the presence of lymphadenopathy and hematologic involvement and is reported to range between 2,5 and 5 years (37,26). In studies with combination therapies, much longer median survival has been indicated (29, 38). Combination therapies used with ECP have become common and among the most often used are interferon-α (IFN-α), total skin electron beam (TSEB), but also methotrexate and bexarotene (39). Several studies of ECP plus IFN-α have been published (38, 40, 41), but evidence is limited as none of these were prospective, randomized controlled trials, included patients with different disease stages and some had more than 2 other combination therapies used (38, 41). In erythrodermic patients with CTCL, fair evidence supports the combination of ECP and TSEB, as data showed a 3-year disease free survival of 81% (32, 42). While most observations support the use of ECP in stages III and IV of CTCL, studies have also been conducted in patients with early stage disease, such as stages IA-IIA, either as mono-therapy or in combination with retinoids, IFN-alpha and other systemic immunostimulatory agents (43). Interestingly, ECP mono- and combination-therapy in patients with early stages of disease disclosed similar response rates, but varied between 33-88% (43, 44). Despite often encouraging data, the long term course of disease and overall survival of patients with early stage CTCL does not appear at present to support the use of ECP in early stages of disease, but should be explored. Only large prospective randomized trials can answer these questions in a satisfactory manner. Predominant theories today explain the therapeutic benefit of photopheresis in CTCL by apoptotic malignant T cells that are phagocytosed by stimulated monocytes (14, 20, 24, 26). Then they are processed and presented by antigen presenting cells which evokes an anticlonotypic response by CD8+ effector cells against the CD4+ neoplastic T cells. On this basis, the reflow of phototreated cells to the patient appears central to ECP's mode of action.

4.2.2. GVHD

Graft-versus-host disease, complicating allogeneic bone marrow transplantation, has been successfully used in the treatment of acute and chronic GVHD for the past 13 years (45, 46, 47). Despite conventional and new therapies for the prevention or treatment of chronic GVHD, this syndrome continues to account for significant morbidity and mortality of affected patients (48). The pathogenesis of chronic GVHD is complex and involves an immune-mediated attack by transplanted donor lymphocytes and auto-reactive phenomena due to activation of immunologic pathways that bear similarities to those involved in several autoimmune disorders (49). Therefore, numerous reports have focused on the use of ECP in chronic steroid/immunosuppressive-refractory GVHD and demonstrated considerable efficacy, especially in patients with cutaneous and mucosal involvement. Response rates are high and vary in reports between 60 and 80% (46, 50, 51). The mechanism by which photopheresis is of therapeutic benefit in chronic GVHD is still unclear. In contrast to other established treatments for GVHD, it seems likely that a change in the regulation of cell function (dendritic cells/T cells), without removal of T cells or other cell fractions including antigen presenting cells, occurs in GVHD. In patients with detectable expanded clonal T cell populations in their peripheral blood, response to ECP treatment is 100% (52), suggesting the induction of an immune response against defined lymphocyte populations by ECP. Cells treated with photopheresis might induce an antigen-specific immune response directed to the pathogenic T cell populations without affecting general immunocompetence. In acute GVHD, a threatened complication with a survival rate of less than 30% (3), ECP has been introduced in patients with a steroid/immunosuppressive-refractory course. Results of these studies are inconsistent, but point to at a very promising adjunct therapy in patients with specific cutaneous and liver involvement (3, 32, 50). Improved survival in these patients could thus easily justify the high costs associated with ECP.

4.2.3. Scleroderma

Systemic sclerosis (scleroderma) is an autoimmune disorder, characterized by abnormal deposits of collagen in the skin and within visceral organs. Prognosis depends on the extent of disease and rates of progression. Therapeutic management in scleroderma is problematic, as prevalence is low and response rates vary according to individual progression of disease. Scleroderma has been linked to chronic graft-versus-host disease due to clinical and biologic similarities, and similar to patients with CTCL and improved response to ECP with higher amounts of clonal T cells in the peripheral blood, likewise results have been reported in patients with systemic sclerosis (53). Responsiveness to ECP in patients showing presence of expanded clonal T-cell populations is higher, though response to ECP does not seem to correlate with the disappearance of the clonally amplified T-cell populations (53). Many reports in the literature show either a beneficial effect of ECP on systemic sclerosis, or no significant benefit/worsening of scleroderma following ECP (54, 55, 56, 57, 58). Specifically improvement of the cutaneous component may override systemic response. Clonality of T cells in peripheral blood has been detected in different nonmalignant conditions (Hingorani), and evidence has been linked to clonal expansion and activation of auto-reactive T cells in certain autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis (60). In the named diseases, again T cells are central to the development of tissue damage and several hypotheses support an antigen-driven clonal expansion of these cells (57, 59). The mechanism of ECP in the successful treatment of scleroderma patients, again is unclear, but points at an abnormal immune activation by means of activated T cells within the peripheral blood and the sites of abnormal collagen production (61). Present experience for this indication suggests that ECP not alone but in combination with other drugs such as cyclophosphamide may improve the observed results.

4.2.4. Solid organ transplant rejection

4.2.4.1. Lung and heart

Allograft survival depends on the control of rejection response against donor molecules of the major histocompatibility complex (MHC). The suppression of the rejection cascade is of major importance for patients receiving an organ transplant. Apart from immunosuppressives and systemic corticosteroids, ECP has been used to reverse allograft rejection (62, 63, 64). The antigens are processed by antigen-presenting cells and presented in the context of their MHC molecules to effector T lymphocytes of the recipient. T cell receptor recognition of the antigenic peptides leads to a stable activation of T cell cytokine gene transcription, which ultimately stimulates the rejection cascade. Different studies have shown that the procedure of photopheresis inhibits the reactivity of the immunological apparatus against transplanted antigens in a specific manner (65). A parallel hypo-proliferative response against graft antigens, due to the generation of specific inhibitor cells and a specific suppression of cytotoxic T cells response versus donor antigens has also been shown (65, 66). The experimental data obtained in the study, support the hypothesis that photopheresis induces an anti-idiotypic response (65), and therefore seems to induce an inhibition of both humoral and cellular rejection after transplantation. Benefit of ECP for lung transplant rejection has been reported, though patient numbers are small (67). In acute lung rejection and in patients developing bronchiolitis obliterans syndrome, stabilization of the airflow obstruction and inhibition of rejection could be obtained without complications (68, 69, 70). A recent report has suggested that ECP might also modulate the number of peripheral T regulatory cells (CD4+ CD25+ T regs), as T reg cell kinetics showed stabilization or a slight increase, in lung transplant patients with clinical improvement following ECP (16).

In cardiac transplantation, photopheresis has gained broad clinical acceptance as an effective therapy for recurrent or persistent rejection (71). Achieved evidence supports the use of ECP in patients with acute cardiac rejection, as the alternative to increasing systemic corticosteroid pulses (72) and in recurrent acute cardiac rejection (73), which is defined as equal or greater than three consecutive episodes of acute rejection. Based on further studies, therapeutic indications have been extended to chronic cardiac rejection and to the prophylaxis of cardiac rejection (64, 71). The impact of photopheresis has been confirmed in a larger study with 36 patients at higher risk for cardiac rejection, who received ECP treatment. The study showed that ECP could reduce the risk of subsequent hemodynamic compromised rejection and /or death from rejection (17).

4.2.4.2. Kidney

ECP has also been reported to be helpful in the management of patients after kidney transplantation, though patient numbers have been small (18, 74). Most results indicate improvement in graft function after ECP in chronic renal allograft rejection as well as in single cases with acute rejection (75, 76), but evidence is poor.

Recently, photopheresis has been reported to be associated with improvement in a disease entity recently described as nephrogenic fibrosing dermopathy (NFD) or so called nephrogenic systemic fibrosis (NSF). This is a rare fibrosing skin disease of unknown etiology occurring in patients with terminal renal disease. The histology of NFD shows an increased number of dendritic cells, fibroblasts and thickened collagen fibers resembling scleromyxedema (77); recent data suggest a close association with the use of Gadolinium (79, 83) in this patient group. Apart from restoration of renal function by renal transplantation or recovery from acute renal failure whenever possible, extracorporeal photopheresis has shown to be of good clinical value even though numbers of patients reported on is small (78, 79).

4.2.5. Other diseases

ECP has been reported to be of benefit in some patients with chronic inflammatory skin diseases, such as lupus erythematodes (80), atopic eczema (81**)** and lichen ruber planus (82). In patients with erosive, therapy-refractory oral lichen ruber planus (LRP), therapeutic options are reduced after first line treatment with corticosteroids. The interest of ECP for severe recalcitrant forms of lichen planus has been raised in view of clinical benefits observed in patients with chronic lichenoid GVHD. Promising albeit preliminary results have shown that ECP shows efficacy in this group of patients (82), and a recent study with 12 patients reported a complete remission of 75% and a partial remission of 25% in patients with refractory LRP (5). Though these reports suggest a possible therapeutic role, at least as a second line option, in the treatment of oral LRP it has to be noted nevertheless, that ECP is expensive and time consuming and patients are immobilized for half a day for each session. However, as oral LRP is a localized disease with high recurrence rates, ECP needs to be confirmed as a useful treatment additive in larger studies, to determine its long-term safety and efficacy.

Another benefit of ECP has been acquainted in patients with blistering diseases, such as epidermolysis bullosa acquisita (84), pemphigus vulgaris and bullous pemphigoid (85, 86, 87). This special group of autoimmune bullous diseases in the skin, has been treated by ECP with substantial benefit (84, 85, 86). Published data on general therapeutic strategies in autoimmune blistering diseases is poor, partly reflecting the rarity of the disease as well as individual courses of disease and pre-therapies in these patients. Use of systemic corticosteroids is among the best established therapies, but the well-known spectrum of side effects and severe relapses following steroid withdrawal, limit their long-term use. ECP has led to partial or complete response in patients with recalcitrant pemphigus vulgaris (86) and also in patients with acquired epidermolysis bullosa (87) without noteworthy side effects. In patients with recalcitrant disease and failure of conventional treatment, ECP offers a well-balanced risk-benefit ratio and makes it a recommendable treatment option for drug-resistant bullous autoimmune diseases.

5. FUTURE PROSPECTS

The fact that ECP has clearly shown, in the clinical setting, the capacity to stimulate apparently opposed immune effects- the up-regulation of an anti-tumor response and the down-regulation of autoimmune diseases or allogeneic immune responses- will contribute to the amplification of therapeutic applications. An exciting important therapeutic improvement could be achieved in children with type I diabetes mellitus. Photopheresis showed an effect in addition to its powerful placebo effect, weak but significant on the disease process at the onset of type 1 diabetes, which was still noted after three years of follow up (88). Preliminary data also supports its use in a selected group of patients with Ulcerative colitis or Chron's disease (89). Future prospects point at more and extended applications of ECP in the therapeutic armamentarium of many other T cell mediated diseases. Randomized controlled studies with statistically significant results are needed to confirm the efficacy of these diseases. Though most studies tried to explain and highlight the exact mode of action, we have to admit that the exact course of immunologic action in patients undergoing ECP still remains uncertain at many levels. In summary, the major advances of photopheresis over conventional therapies for CTCL, GVHD and autoimmune diseases, its selectivity for the pathogenic clones via a non-toxic, steroid sparing therapeutic alternative makes ECP a unique, attractive and promising therapy.

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Abbreviations: CTCL: Cutaneous T - cell lymphoma, ECP: Extracorporeal photopheresis or extracorporeal photoimmunotherapy, FDA: Food and Drug Administration, the Consumer Protection Agency of the US Government which monitors medical devices, foods, drugs, biologics, veterinary medicine and more, GVHD: Graft - versus - host - disease, INF: Interferon, MHC: Major histocompatibility complex, MOP: Methoxy psoralen, NFD: Nephrogenic fibrosing dermatopathy , same as NSF, NSF: Nephrogenic systemic fibrosis, LRP: Lichen ruber planus, PUVA: a therapy combining the administration of the photosensitizer psoralen and UV-A irradiation, TSEB: Total skin electron beam , T regs: T regulatory cells

Key Words: Photopheresis, Photoimmunotherapy, Cutaneous T cell lymphoma, GVHD, Transplant rejection, Scleroderma, Review

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