



Extracorporeal photopheresis: is the CELLEX equivalent to the UVAR-XTS

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Extracorporeal photopheresis (ECP) is an immunotherapy which is FDA approved for patients with cutaneous T cell lymphoma (CTCL) but which has been used extensively in patients with solid organ transplant rejection and acute and chronic graft-vs-host disease (GVHD) associated with allogeneic stem cell transplantation. ECP involves apheresis to separate a buffy coat containing peripheral blood mononuclear cells (MNCs) which are then exposed in a collection bag to 8-methoxypsoralen, a DNA intercalating agent and then passed through a thin plastic plate placed between two UVA light sources to expose the cells uniformly to ultraviolet light. The treated cells are then reinfused into the patient. The ECP procedure was first approved by the FDA in 1988 based on a study by Edelson *et al.* which demonstrated a response rate of 73% in patients with erythrodermic CTCL treated with the original UVAR system (1). The UVAR was modified to the UVAR-XTS which was approved in 1999. The UVAR-XTS ECP device collects MNCs in a collection bag, then 8-methoxypsoralen is added cells and then they are treated with UVA light. The treated cells are collected in a bag and then reinfused as an intravenous bolus. In 2009, a new device (CELLEX) was designed to provide a continuous flow circuit for collection, treatment, and reinfusion (2). Both the UVAR-XTS and the CELLEX are used for ECP treatments for GVHD, transplanted organ rejection, and GVHD, but to date there have been few studies comparing patient outcomes with the continuous CELLEX *vs.* intermittent UVAR-XTS cell collection and processing. To determine whether outcomes were similar between the two devices, Afzal *et al.* have conducted a retrospective review of GVHD patients

undergoing ECP with either the UVAR or the CELLEX device and they recently reported results in *Transfusion* demonstrating comparable safety and efficacy in patients with chronic GVHD (3).

Device characteristics

The UVARTMXTSTM photopheresis system (TherakosTM, Exton, PA, USA) is an intermittent flow centrifugation system which collects the MNC concentrate using an intermittent flow leukapheresis technique. During the collection phase, which takes approximately 90–150 minutes, up to 1.5 L of whole blood is processed over three to six cycles. Separation of MNCs from whole blood is accomplished by centrifugation using either a 125 mL (small) or 225 mL (large) Latham bowl (Haemonetics Corporation, Braintree, MA, USA). The smaller bowl is used for patients with lower body weight, anemia, or hemodynamic instability who may not be able to tolerate larger shifts in intravascular volume. The centrifugation aims to reduce or eliminate as many red blood cells from the buffy coat as possible, as the RBC in the collection bag may shield the MNCs from the UVA in the treatment chamber. The MNCs collected in the bowl are exposed to 8-methoxypsoralen which is injected into the bag and the dose is calculated based on the volume of cells in the collection [MNC product volume (mL) × 0.017 = mL of 8-methoxypsoralen (UVADEXTM)]. The total number of cells treated with each ECP procedure varies depending on the collection but is approximately 10% of the total body

peripheral blood MNCs. Treating children on the UVAR has posed challenges due to the amount of extracorporeal volume, but techniques have been proposed using fluid boluses which have allowed the treatment to be used in low body weight individuals (4-6).

The Cellex™ (Therakos Inc., Exton, PA, USA) device was FDA approved as replacement for the UVAR. Unlike the UVAR, it uses a continuous flow system to collect peripheral blood MNCs into the same Latham bowl where they undergo centrifugation to separate the buffy coat and then the cells are treated with 8-methoxy psoralen and passed into the photoactivating chamber by continuous flow. The cells can then be directly reinfused into the patient using a “two needle” technique. The advantage of this system is that it reduces the *ex vivo* blood volume, thus facilitating treatment of low body weight patients and those who may experience hemodynamic compromise with the XTS system. Bisaccia *et al.* measured the treatment times and treatment characteristics for adult patients undergoing treatment with the CELLEX and reported that the average extracorporeal blood volume was 216–266 cc (2). Reinfusion is accomplished either through a separate intravenous line or through the same line if possible. Treatment times were shorter (73 minutes) for “two needles” treatments compared to patients treated with one intravenous access (103 minutes), and there were unanticipated adverse events with the CELLEX. Whittle *et al.* compared XTS and CELLEX treated patients and reported an average treatment time of 122 minutes with the CELLEX and 172 minutes with the XTS device (7). Kapadia *et al.* reported a series of children treated with CELLEX and found that it was faster, performed better in terms of MNC collection, and required less TPA for line occlusions (8).

Another advantage of the CELLEX is that patients with a lower hematocrit can be treated without transfusion of packed red blood cells in advance. In one study of 6 adult GVHD patients with hematocrits between 25% and 28.9% who received ECP on the CELLEX system without transfusions in advance, there were no adverse effects and the treatments were well tolerated (9). This is especially relevant for patients with GVHD who often have accompanying cytopenias post allogeneic transplant.

Comparing efficacy between CELLEX and XTS

Although it is unclear how many MNCs need to be treated with each ECP procedure and whether cell number or cell composition correlates with clinical response, several

studies have reported characteristics of the cell collections with the two devices. Piccirillo and colleagues compared the two devices in 28 adult patients with GVHD treated with the CELLEX (10). The median collection efficiencies for MNCs and total nucleated cells were 62.3% and 31.2% respectively and was comparable to the UVAR system. Liu *et al.* compared collection efficiencies between the two devices in 8 GVHD patients treated with UVAR and 16 with CELLEX (9). The CELLEX patients had better enrichment of lymphocytes and monocytes in the collection than the UVAR patients (by 5.3 *vs.* 2.3 fold for lymphocytes, 5.9 *vs.* 2.1 fold for monocytes). The impact of higher cell collection and higher number of treated cells on outcome is still unclear but higher cell yields will facilitate shortening of treatment times for the procedure.

Other relevant cell populations which have been studied in ECP treated patients include neutrophils and monocytoïd dendritic cells. Franklin *et al.* demonstrate a higher number of neutrophils in the collection with CELLEX and have shown that ECP treated neutrophils have a reduced capacity to release inflammatory cytokines, suggesting that the increased number treated with CELLEX may be an advantage with respect to immunosuppressive effects of the treatment in patients (11,12). Ni *et al.* evaluated the generation of monocytoïd dendritic cells in patients with CTCL who were undergoing ECP on the Cellex device (13). They had previously reported that mDCs were increased in CTCL patients treated with the XTS device. They reported increasing numbers of mDC in the CELLEX treated patients, similar to what was observed in the XTS patients, suggesting that the mechanism of action was similar between the two devices.

Retrospective clinical studies

To date, there has been no prospective randomized trial comparing the clinical efficacy of the CELLEX *vs.* the XTS in any disease setting. Data are available from retrospective studies and individual center experiences. Whittle *et al.* reported a series of 50 patients with steroid refractory cGVHD undergoing photopheresis treatment with either the XTS or the CELLEX (7). The patients were reviewed for endpoints including steroid withdrawal or reduction over 12 months. There were 51 patients treated with the XTS and 50 treated with CELLEX (7). Overall response in this study was excellent, with a 70% response rate at 6 months and with steroid reduction in 85% of patients. Responses occurred in all organ sites for both groups but

there was a trend toward a better skin response in the patients treated with CELLEX. Interestingly there was a better outcome in steroid sparing ($P=0.03$) and steroid withdrawal ($P=0.01$) in patients treated with the XTS system and that group experienced fewer complications and infections. Differences in patient characteristics and immunosuppression regimens between the two groups may account in part for these observed outcomes.

Afzal *et al.* recently published a retrospective analysis of outcomes of patients with steroid refractory GVHD who were treated with either the XTS or the CELLEX device. Treatments were performed weekly for 4 weeks, followed by two procedures biweekly for four times, then two procedures monthly $\times 4$ for a total of 24 procedures (3). All patients treated after 2016 were treated on the CELLEX. Of 146 patients, 77 were treated with CELLEX and 69 with XTS. The groups differed in several important prognostic variables, with more patients in the XTS group having had ablative conditioning, higher number of organs involved with GVHD, and higher number of immunosuppressive agents at the time that photopheresis was started. While outcomes with respect to steroid reduction were better with the CELLEX group (35% *vs.* 18%), these differences disappeared when potential confounding factors were taken into consideration (age, sex, year of SCT, type of transplant and conditioning regimen, number of organs involved, number of immunosuppressant agents and steroid dose). Given that these cofactors may significantly impact outcome for patients with GVHD, this analysis provides the most precise data with respect to the outcomes of the two devices when compared in a similar patient population. Of interest in this report is the inclusion of patients with acute GVHD who had benefit equal to that of the cGVHD patients, despite an otherwise worse overall outcome for these patients in general.

These two retrospective studies comparing outcomes for patients with GVHD have somewhat disparate results, but it is difficult to compare the data given the limitations of both studies. First, there are differences with respect to risk factors associated with GVHD risk between the two studies. Both are retrospective and subject to bias with respect to selection of therapy, steroid taper schedule, and observation of objective responses. Second, any comparison of XTS *vs.* CELLEX in GVHD suffers from the historical bias due to machine availability. Standards of care for allogeneic stem cell transplant patients have significantly changed over the last 20 years with availability of better immunosuppression regimens and more active agents for both immunosuppression and transplant related morbidities

such as infections. Therefore, only a randomized trial in this population would shed light on whether either treatment is superior, but existing data suggests that both treatments are likely equivalent with respect to efficacy for GVHD.

ECP is also used extensively in organ transplantation. Chionis reported a series of patients with bronchiolitis obliterans after lung allograft who were treated for rejection with either the XTS or the CELLEX machine (14). There were 44 patients from a Registry series and 60 from a prospective clinical trial of CELLEX therapy. When compared, there was no difference in response between the two instruments (UVAR XTS: 77% *vs.* CELLEX: 89%; $P=0.36$) in change in FEV1 and survival was similar between the two instruments despite a trend toward a higher early mortality (34% *vs.* 17%, $P=0.054$) in the CELLEX patients. As of now, there are no other data comparing the two devices in other solid organ transplant populations.

Mechanism of action of ECP—is there a difference?

The mechanism of photopheresis in GVHD is not clearly understood but several investigations over the last ten years have shed light on different immunomodulatory and effector cell mediated mechanisms which may play a role in clinical outcomes. Gorgun *et al.* first demonstrated in 2002 that photopheresis treatment in the setting of chronic GVHD was associated with modulation of dendritic cell populations and dendritic cell maturation along with induction of a tolerogenic cytokine milieu (15). The expression of IL-10 and reduction in costimulatory molecule expression on dendritic cells was subsequently shown by other groups (16).

One major breakthrough in the understanding of the mechanism came from *in vitro* work with a mock ECP device by Edelson *et al.*, who discovered that the plastic plate played a major role in the conversion of immature to mature dendritic cells (17). Immature dendritic cells passing over the ECP plates adhered transiently to plasma proteins, including fibronectin, adsorbed to the plastic ECP plate and activated signaling pathways that initiate monocyte-to-DC conversion (17,18). Platelets have also been shown to play a role by adhesion of platelet $\alpha 2\beta 3$ and $\alpha 5\beta 1$ integrins to the fibronectin and activation of P-selectin (18). The P-selectin then attracts monocytoïd cells via P-selectin glycoprotein ligand, which stimulates the maturational pathway (19).

Studies of these effector populations and mechanistic evaluation of the treatment on the CELLEX compared to the XTS remains to be elucidated. Ni *et al.* evaluated the

generation of mature dendritic cells in patients treated on the CELLEX machine (13). In this study bloodwork was obtained at baseline, day 2, then months 1,3, and 6 on 20 patients with CTCL who were treated with the CELLEX device, and data was compared to an earlier cohort treated with the XTS device. The investigators found that CD209+ monocytoid dendritic cells increased 4.8-fold after a CELLEX treatment, similar to what was earlier observed with the XTS device (20). Further mechanistic studies are needed to confirm with certainty that the components of effector cell engagement and modulation by the treatment in the CELLEX device are identical to those observed with the UVAR system.

Summary

From the time of the first report of efficacy of extracorporeal photochemotherapy in patients with CTCL, a rare type of lymphoma, the use of photopheresis and our understanding of its mechanism of action have grown tremendously. With the evolution of the understanding of the mechanism of action and the range of diseases for which it can be applied has been a change in the technology to move from an intermittent buffy coat processing and reinfusion technology to a continuous flow system which has optimized treatment time and extracorporeal volume issues for low body weight patients. Retrospective studies, mostly conducted in patients with GVHD, have shown equivalence between the two devices with respect to defined and measured clinical outcomes, but there as yet been no randomized clinical trial to dissect potential nuances of the differences between the two devices which may be favorable to a specific subset of patients or disease entities. Now that mechanistic studies have evolved to the point where we are able to elucidate specific pathways, effector populations, and immunomodulatory changes associated with the treatment, a detailed *in vivo* mechanistic study is indicated to confirm that the two devices are, in fact, immunomodulatory equivalents.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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