Extracorporeal Photopheresis Meeting

The Faculty Club, Leuven, Belgium; 9th November 2016

Chair: Hélène Schoemans, Department of Haematology, UZ Leuven

On the 9th November 2016, Mallinckrodt Pharmaceuticals (Commercial) hosted an educational evening in Leuven, Belgium. This photopheresis conference was focussed on immunotherapy, specifically in the treatment and management of acute and chronic graft versus host disease (aGvHD and cGvHD).
Extracorporeal Photopheresis (ECP): The Belgian Experience

Hélène Schoemans, Department of Haematology, UZ Leuven

In the opening session, Dr Hélène Schoemans discussed how extracorporeal photopheresis (ECP) is currently being used in Belgium for a variety of disease states.

Extracorporeal photopheresis is a cell-based immune modulatory therapy, which takes place outside of the body in three phases (Figure 1).

**Figure 1. Extracorporeal photopheresis with the THERAKOS® CELLEX® Photopheresis System**

Open and closed ECP methodologies are used in clinical practice. Whereas the open (“multi-step”) procedure can be lengthy, as the patient’s blood must be sent to the laboratory where separate devices are used for cell separation and drug photoactivation, the closed system (“one-step” or “in-line”) can take as little as 1.5 to 2.5 hours. In the closed system, the cell separation, drug photoactivation and reinfusion stages are fully integrated within a single medical device.

There are currently 10 centres in Belgium treating patients with ECP; however, only 4 centres are offering closed system ECP via the THERAKOS® CELLEX® Photopheresis System: Cliniques Universitaires Saint-Luc, Brussels; Antwerp University Hospital, Antwerp; Sart Tilman, Liège; and UZ Leuven, Leuven.

Dr Schoemans’s personal communications with treating physicians in these centres indicate that of the 52 patients treated with ECP in the above 4 centres from November 2014 to November 2016, the majority (88%) were treated for cGVHD, with 10% treated for aGVHD (2% for Sézary syndrome; 1 patient). Of these, 88% were adults and 12% were patients with low body weight.

In Leuven, 7 patients have been treated for cGVHD affecting the skin and/or lung between November 2015 and August 2016. The usual treatment schedule was 2 days every 2 weeks, for a total of 3 months. In general, ECP treatment has been well tolerated; one patient experienced a disease flare, and treatment was discontinued. However, once the patient resumed ECP treatment, this quickly resolved. One patient was able to receive a lung transplant after 6 months of therapy.

Unfortunately, the CELLEX® System is not yet reimbursed in Belgium. Therakos provided support for the treatment of cutaneous T cell lymphoma (CTCL) patients via the solidarity fund, before their first unsuccessful filing attempt in 2010. A second attempt to file was made in March 2016, after Therakos began reviewing the cost of treating CTCL patients at the point at which they would begin to receive ECP treatment. Despite lack of success in securing reimbursement, the feedback from the regulatory authorities was positive.

**First Session: Understanding Acute GvHD – How Does ECP Help?**

Andy Gennery, Paediatric Immunologist; Clinical Reader/Consultant in Paediatric Immunology and Haematopoietic Stem Cell Transplantation, Director of the Northern Deanery Academic Foundation Programme, and Child Health Research and Development Lead, Institute of Cellular Medicine, Great North Children’s Hospital, Newcastle Upon Tyne, UK

**Acute GvHD: Lessons from Primary Immunodeficiency**

Dr Andy Gennery manages patients with primary immunodeficiency (PID), pre- and post-transplant. In PID, haematopoietic stem cell transplantation (HSCT) is used in order to achieve immunoreconstitution.

The mechanism of action of ECP is, as yet, unconfirmed, although it appears to act in an immunomodulatory fashion that may involve regulatory T lymphocytes and dendritic cells. Dr Gennery’s work with PID suggests that ECP may initiate a process that ultimately allows thymic recovery and restoration of thymopoiesis.²

**T Cell Reconstitution**

Following HSCT, two waves of T cell reconstitution take place, with the second wave lasting approximately 120 days.³

1. Peripheral expansion of pre-formed donor T lymphocytes
2. New T lymphocytes are formed (thymopoiesis) and donor-derived stem cells with T lymphocyte progenitors are “tolerised” in the recipient’s thymus
Müller and colleagues examined the reconstitution of CD4+ cells in patients with severe combined immunodeficiency (SCID) who received T cell-depleted stem cells with or without prior chemotherapy conditioning. In both cases, T cells remained absent for the first 4 to 5 months, before the appearance of CD4+ cells. However, in those patients who had received preconditioning, the recovery rate of CD4+ cells in the following months was slower than in patients without conditioning. These findings suggest that pre-transplant conditioning may reduce the functioning of the thymus.

Central and peripheral tolerance are the processes that ensure developing T cells are non-reactive to self. Autoimmune regulator (AIRE) deficiency impairs the function of the medullary thymic epithelial cells (mTECs), so autoreactive T cells can escape from negative selection, resulting in autoimmunity.

Regulatory T lymphocytes (Tregs) are involved in establishing peripheral tolerance. Patients with PID disorders often have reduced numbers of regulatory T cells. For example, immune dysregulation-polyendocrinopathy-enteropathy-X-linked (IPEX) syndrome is caused by mutations in the FOXP3 gene, which is a critical transcriptional regulator involved in the development of CD4+CD25+ Tregs. Omenn syndrome is often mistaken for GvHD; the majority of cases to date have hypomorphic mutations in the genes involved in VDJ recombination, which results in abnormal thymic development and aberrant clonal T cell expansion.

**Thymic Damage**

Thymic damage is thought to occur in patients before HSCT transplant due to a combination of their pre-existing condition and the treatments they may have received, such as total body irradiation and chemotherapy conditioning. After the transplant has taken place, the patient may develop GvHD. Corticosteroids are the first-line treatment for the disease, but they have potent immunosuppressive effects, which, along with the acute GvHD itself, may impair thymopoiesis further.

The conditioning regimens and pre-existing disease lead to an increase in pro-inflammatory cytokines, which activate the host antigen-presenting cells (APCs). Following the transplant, the donor T lymphocytes become activated by the host APCs, before proliferating, inducing the transcription of further cytokines and moving to the skin, gut and liver where cytotoxic T lymphocytes and NK cells cause damage to the host tissues. Findings in a mouse model have demonstrated that GvHD results in loss of mTECs in the damaged thymus and impaired expression of tissue-restricted antigens. Even subclinical GvHD, which may only require treatment with topical steroids, damages the thymus and has significant impact on thymopoiesis.

**Figure 2. Potential effect of ECP**

Unfortunately, the immunosuppressive drugs used for first-line treatment of aGvHD are all associated with serious adverse events. Glucocorticoids are the gold standard, but research suggests that they may add to the disruption of thymic function. In an avian model, intensive steroid treatment was shown to reduce the number of thymocytes and the number of T cells being exported to the periphery. The potential effect of ECP is illustrated in Figure 2.

**Potential Effect of ECP**

The exposure of mononuclear cells to B-MOP and UVA radiation induces apoptosis of treated leukocytes (including activated T lymphocytes), but does not explain the full effects of ECP. There is evidence that ECP can induce monocytes to enter the dendritic cell differentiation pathway and induces Tregs, but further research is needed to elucidate more information about these mechanisms.

The immunomodulatory effect of ECP is a key advantage of this treatment, as it allows for reduction of conventional immunosuppressive treatments. Treatment is generally well tolerated, with few side effects. In addition, by selectively targeting the pathogenic alloreactive T lymphocytes, ECP promotes a tolerogenic environment and preserves the graft-versus-leukaemia effect. When used for the treatment of aGvHD, ECP may play a positive role in thymic recovery and restoration of thymopoiesis, thereby helping rebalance the mechanisms involved in the development of adaptive immunity.

Currently, ECP is still recommended as a second-line treatment for aGvHD, after corticosteroids. However, there are ongoing studies that may provide answers as to whether ECP could be used at an earlier stage. Understanding the mechanism of action of ECP would enable physicians to identify those patients who will respond to therapy, and may allow delivery systems to be improved in the future.

**Second Session: Role of ECP in the Management of Chronic GvHD**

**Arun Alfred, Consultant Haematologist, The Rotherham Foundation Trust**

Dr Alfred joined the meeting to discuss how ECP is being used in Rotherham, UK, for the treatment of patients with GvHD.

GvHD is a possible complication of an allogeneic haematopoietic stem cell transplantation. The classification of GvHD as “acute” or “chronic” is now thought to be determined by the clinical manifestations of disease, and not the time after transplantation (previously, day 100 post-transplantation was used to separate the acute and chronic versions of the disease). Chronic GvHD is a major cause of non-relapse mortality and has a prevalence of 25-80% in long-term survivors. It can manifest in several different areas of the body causing infections, disability, pain, and has a negative impact on patients’ symptom score. Dr Alfred explained that his transplant patients are often unprepared for the potential consequences of GvHD and are affected to the point that they may voice their desire to have never received a transplant for their initial disease.

Chronic GvHD has a median time of onset of 4 to 6 months, with 5-10% patients diagnosed more than 1 year after their transplantation. Immunosuppressant treatment is required for a median of 2-3 years, with 15% of patients who were alive (without recurrent malignancy) still receiving immunosuppressive therapies at 7 years.
The team in Rotherham evaluated 219 consecutive patients who were treated with ECP for cGVHD between 1996 and 2012. Overall response was measured at Weeks 14, 28, 56 and 112; patients who showed an improvement in National Institutes of Health (NIH) organ score (≥25% for Rodnan's skin score) and/or ≥50% reduction in steroid dose were classified as responders and all other patients were classified as non-responders.13

The skin showed the maximal response (91/134 [68%] responders at Week 14), followed by the oral mucosa (42/96 [67%]), and response to ECP was shown to be an important predictor of improved patient survival (Table 1).

### Table 1. Effect of response to ECP on patient survival

<table>
<thead>
<tr>
<th>Time Point (Week)</th>
<th>Category</th>
<th>n</th>
<th>Hazard Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Responder vs. non-responder</td>
<td>150</td>
<td>0.408 (0.223-0.746)</td>
<td>0.003</td>
</tr>
<tr>
<td>28</td>
<td></td>
<td>138</td>
<td>0.412 (0.199-0.856)</td>
<td>0.014</td>
</tr>
<tr>
<td>56</td>
<td></td>
<td>112</td>
<td>0.345 (0.137-0.886)</td>
<td>0.018</td>
</tr>
<tr>
<td>112</td>
<td></td>
<td>88</td>
<td>0.383 (0.109-1.344)</td>
<td>0.120</td>
</tr>
</tbody>
</table>

Red font indicates statistical significance.

The median duration of ECP treatment was 57 weeks, with a range of 1–585 weeks. Infections were the major cause of death, but the infection rate was no higher than that seen with other treatments. Safety and tolerability of the treatment were consistent with previous reports.14, 15 In particular, ECP had a “steroid sparing” effect, which has been identified as important beneficial effect for patients with cGVHD, reducing the problems associated with immunosuppression.16, 17

Although the team identified some predictors of poor survival (high bilirubin ≥2 mg/dl; thrombocytopenia (≤100 x10⁹/L); steroid dose ≥0.5 mg/kg), there were no reliable patient characteristics that could predict the response to treatment. In the absence of any predictive factors for response to ECP treatment, the management of cGVHD should focus on working with an individual patient’s response to therapy (with the ultimate goal of clinical tolerance). This requires continuous recalibration of immunosuppressive treatment as the disease manifestations improve or worsen, in order to treat the patient optimally.

### ECP and Symptom Score

From January 2011 to January 2015, 68 patients receiving ECP with GvHD (overlap or clear-cut disease) were included in a study which used the Lee cGvHD symptom scale18 to examine health-related quality of life at 0, 6, 12 and 18 months. These data are currently unpublished.

At all time points, there was an improvement in symptom scores compared to the start of treatment, and a statistically significant reduction in the steroid dose. Patients who started with high bilirubin or a low platelet count had no improvement in symptom score, but did have a significant reduction in their dose of steroids, although the statistical significance of this was difficult to assess given the low number of patients. In addition, a quarter of all patients continued to show an improvement from 6 to 18 months.

The Rotherham ECP service is a shared care model between the national bone marrow transplant centres and the dermatology service (the Regional Skin Cancer Network). The Rotherham team has developed a patient passport to capture details of the treatment plan to ensure that patient care remains consistent. In the UK there are several, similar, local protocols, and a new consensus document has been developed that may bring together expertise and allow consistency of care for all patients with cGVHD.19

### References


CAUTION: READ THE THERAKOS® UVAR XTS® or THERAKOS® CELLEX® PHOTOPHERESIS SYSTEMS' OPERATOR'S MANUAL PRIOR TO PRESCRIBING OR DISPENSING THIS MEDICATION. DO NOT INJECT DIRECTLY INTO PATIENTS.

For the THERAKOS® Photopheresis Procedure:

INDICATIONS
THERAKOS® UVAR XTS® and THERAKOS® CELLEX® Photopheresis Systems are indicated for the administration of photopheresis.

CONTRAINDICATIONS
THERAKOS® Photopheresis is contraindicated in patients possessing a specific history of a light sensitive disease. THERAKOS® Photopheresis is contraindicated in patients who cannot tolerate extracorporeal volume loss or who have white blood cell counts greater than 25,000 mm$^3$.

THERAKOS® Photopheresis is contraindicated in patients who have coagulation disorders or who have had previous splenectomy.

WARNINGS AND PRECAUTIONS
THERAKOS® Photopheresis treatments should always be performed in locations where standard medical emergency equipment is available. Volume replacement fluids and/or volume expanders should be readily available throughout the procedure. Both men and women should take adequate contraceptive precautions both during and after completion of photopheresis therapy. Safety in children has not been established.

Adverse Events
Hypotension may occur during any treatment involving extracorporeal circulation. Closely monitor the patient during the entire treatment for hypotension. Transient pyretic reactions, 37.7–38.9°C (100–102°F), have been observed in some patients within six to eight hours of reinfusion of the photoactivated leukocyte-enriched blood. A temporary increase in erythroderma may accompany the pyretic reaction. Treatment frequency exceeding labeling recommendations may result in anemia. Venous access carries a small risk of infection and pain. Methoxsalen should be used only by physicians who have special competence in the diagnosis and treatment of cutaneous T-cell lymphoma and who have special training and experience with the THERAKOS® UVAR XTS® or THERAKOS® CELLEX® Photopheresis Systems.

For methoxsalen used in conjunction with THERAKOS® Photopheresis:

INDICATIONS
UVADEX™ 20 MICROGRAMS/ML SOLUTION FOR BLOOD FRACTION MODIFICATION is used in conjunction with either the THERAKOS® CELLEX® or the THERAKOS® UVAR XTS® Photopheresis System, in the palliative treatment of the skin manifestations (patch plaque, extensive plaque, erythroderma) of advanced stage (T2 – T4) cutaneous T-cell lymphoma (CTCL), only in patients who have not been responsive to other forms of treatment, (e.g. puvatherapy, systemic corticosteroids, caryolsyn, interferon alpha).

CONTRAINDICATIONS
Methoxsalen is contraindicated in patients exhibiting idiosyncratic or hypersensitivity reactions to methoxsalen, psoralen compounds, or any of the excipients. Methoxsalen is contraindicated in patients with co-existing melanoma, basal cell or squamous cell skin carcinoma. Methoxsalen is contraindicated in sexually active men and women of childbearing potential unless adequate contraception is used during treatment, and during pregnancy and lactation. Methoxsalen is contraindicated in patients with aphakia, because of the significantly increased risk of retinal damage due to the absence of a lens.

WARNINGS AND PRECAUTIONS
Special care should be exercised in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosensitizing agents. Skin burns or premature aging may occur if protective precautions are not taken. Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic. Because the dose with liquid methoxsalen is about 200 times less than with PUVA therapy and the skin is not exposed to high cumulative doses of UVA light, the risk of developing skin cancer following this therapy may be lower. Patients should be told emphatically to wear UVA absorbing, wrap-around sunglasses for twenty-four (24) hours after methoxsalen treatment. They should wear these glasses any time they are exposed to direct or indirect sunlight, whether they are outdoors or exposed through a window.

Safety in children has not been established.

ADVERSE EVENTS
Side effects of photopheresis were primarily related to hypotension secondary to changes in extracorporeal volume (>1%).

For Additional Safety Information please refer to our website www.therakos.co.uk

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