Photopheresis in lung transplant rejection

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Introduction

- Bronchiolitis Obliterans Syndrome (BOS) in lung transplant
- Photopheresis in BOS
- PDH hospital experience
  - Apheresis procedures
  - Clinical results
Bronchiolitis Obliterans Syndrome (BOS)

- Chronic graft rejection in lung transplant
- 60% of LT patients develop BOS in the 5 first years after transplant
- Increased risk of death and re-transplant
  - Leading cause of death after the 1st year after transplant
  - Causes 20-30% deaths
- BOS Survival median 3-4 years (range 0-9 years)
Bronchiolitis Obliterans Syndrome (BOS)

- Subepithelial inflammatory and fibrotic narrowing of the bronchioles

- After HSCT or solid organ transplantation, autoimmune disorders, viral respiratory infection, chronic GERD, air pollutants (final common pathway).

- Alloimmune reaction: direct T-cell-mediated injury of graft structures, circulating antibodies to donor HLA molecules
Bronchiolitis Obliterans Syndrome (BOS)

- Progressive Dyspnea
- Non-productive Cough
- Persistent airflow obstruction
- Declining Forced expiratory volume in 1 second (FEV-1)
Introduction

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Photoapheresis

- Second-line treatment after failure inmunosupressive treatment in the treatment of BOS
  - High-dose Methyl-prednisolone
  - Methotrexate
  - ATG
  - Alemtuzumab
<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cutaneous T-cell lymphoma; mycosis fungoides; Sezary syndrome (erythrodermic)</td>
<td>1B—strong recommendation, moderate quality evidence</td>
</tr>
<tr>
<td></td>
<td>Cardiac transplant (cellular or recurrent rejection)</td>
<td>1B—strong recommendation, moderate quality evidence</td>
</tr>
<tr>
<td></td>
<td>Chronic graft versus host disease (GVHD), skin</td>
<td>1C—strong recommendation, low quality evidence</td>
</tr>
<tr>
<td></td>
<td>Acute GVHD, skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung allograft rejection: bronchiolitis obliterans syndrome (BOS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac transplant (rejection prophylaxis)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Psoriasis</td>
<td>2A—weak recommendation, high quality evidence</td>
</tr>
<tr>
<td></td>
<td>Scleroderma (progressive systemic sclerosis)</td>
<td>2B—weak recommendation, moderate quality evidence</td>
</tr>
<tr>
<td></td>
<td>Crohn’s disease (CD)</td>
<td></td>
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<tr>
<td></td>
<td>Cutaneous T-cell lymphoma (nonerythrodermic)</td>
<td>2C—weak recommendation, low quality evidence</td>
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<tr>
<td></td>
<td>Nephrogenic systemic fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pemphigus vulgaris</td>
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</tbody>
</table>

aDisorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.

bDisorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.

cOptimum role of apheresis therapy is not established. Decision making should be individualized.
Photoapheresis

- Lymphocytes treated with a photosensitizing agent
  - 8-Methoxypsoralen
- Irradiation with UVA light
- Nucleated cells apoptosis
- Reinfusion to the patient
- Immunomodulation
Introduction

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Objectives

Evaluate ECP procedures in lung transplantation patients with obliterative bronchiolitis refractory to IS therapy.
Patients and procedures

• March 2012 to Nov 2014  32 months

• Patients  16

• Procedures  302
Patients

<table>
<thead>
<tr>
<th>N= 16</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median)</strong></td>
</tr>
</tbody>
</table>
Lymphocyte collection

Photo-inactivated lymphocytes infusion

Lymphocytes
Photo-inactivativation
Lymphocyte collection

* Two per week for the first month
* Two every two weeks for 3 months
* Two per month
Number of photopheresis procedures per patient

Median 21 procedures per patient
Machines for lymphopheresis
Venous access
## Lymphocyte Collection

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collection time (average, SD)</td>
<td>206(29) min</td>
</tr>
<tr>
<td>Blood volume average (SD) ml</td>
<td>4205(788)</td>
</tr>
<tr>
<td>Blood-volume processed average (SD) ml</td>
<td>8074 (2161)</td>
</tr>
<tr>
<td>Number of Patient blood volume processed. Median (range)</td>
<td>1.95 (0.2-3.1)</td>
</tr>
<tr>
<td>ACD used ml (average (SD))</td>
<td>753 (194)</td>
</tr>
<tr>
<td>Average flow ml/min average (SD)</td>
<td>47 (25)</td>
</tr>
</tbody>
</table>
Adverse events in photopheresis

March 2012 to Nov 2014
299 procedures in Lung Transplant patients
Product features (by machine)
Lymphocyte collection

Photo-inactivated lymphocytes infusion

47 min

Lymphocytes
Photo-inactivativation
Photoinactivation

UVA illumination + MNC collection + 8-MOP addition = Theraflex-MacoPharma®

8-MOP 0.2 umg/ml
Lymphocyte collection

Photo-inactivated lymphocytes infusion

4:14 min

Lymphocytes Photo-inactivatation
Clinical evaluation & response
Patients

<table>
<thead>
<tr>
<th></th>
<th>N = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median)</strong></td>
<td>42.8 (19.4-64.1) years</td>
</tr>
</tbody>
</table>
Clinical evaluation

- FEV1 measured every two ECP sessions

- Response criteria were:
  - Stabilized FEV1
  - Decreased rate of FEV1 decline (compared to the previous three months)
FEV-1 evolution

Photopheresis treatment
<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>N=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from transplant to photoapheresis treatment</td>
<td>58.4 (29.4-182.8)</td>
</tr>
<tr>
<td>Months (median-range)</td>
<td></td>
</tr>
<tr>
<td>Time on ECP treatment</td>
<td>5.8 (0.1-29.8)</td>
</tr>
<tr>
<td>Months (median-range)</td>
<td></td>
</tr>
<tr>
<td>Time to <strong>clinical response</strong> since first procedure</td>
<td>3.7 (0.03-10.9)</td>
</tr>
<tr>
<td>Months (median-range)</td>
<td></td>
</tr>
<tr>
<td>Follow-up: Months (median-range)</td>
<td>7.6 (0.03-32.8)</td>
</tr>
<tr>
<td>Clinical improvement n(%)</td>
<td>1 6.25%</td>
</tr>
<tr>
<td>Stable disease n(%)</td>
<td>11 68.75%</td>
</tr>
<tr>
<td>No response n(%)</td>
<td>4 25%</td>
</tr>
<tr>
<td>Re-Transplantation n(%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Deaths n(%)</td>
<td>3 (18.7%)</td>
</tr>
</tbody>
</table>
Response Survival function

Months to response

Survival Function
Censored
Survival from photoapheresis

months from first apheresis
Conclusions

Extracorporeal photopheresis:

· Is a well tolerated procedure
· It can stabilizes BOS progression and delay re-transplantation in patients with refractory BOS to other immunosuppressive therapies.
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- HPHM Transfusion Service. Hematology Dptm.
  Resident HPHM Transfusion Service. Hematology Dptm.
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HRCT. “Mosaic attenuation” pattern in BOS
Bronchiolitis Obliterans Syndrome (BOS)

- Plain chest radiograph: N, hyperinflation, increased linear or reticular markings of airway wall thickening

- HRCT in expiration: “mosaic attenuation” pattern (air trapping).

- Lack of ground-glass opacities.