Photopheresis in Acute Graft-versus-Host Disease

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Acute GvHD is Serious Complication of Allo HCT

- **Challenge**: GvL effect vs. morbidity and mortality due to severe GvHD
- GvHD has significant negative impact on survival
- **Challenge**: Efficacy vs toxicity of IS
Steroids as Established First-Line Therapy of Acute GvHD

Response to Steroids

NRM and OS

MacMillan et al, Blood 2010

Van Lint et al, Blood 2006
ECP in Acute Steroid-Refractory GvHD
Development of ECP for Clinical Use

- 1981: First ECP
- 1987: ECP Approval for CTCL
- 1994: ECP in Chronic GvHD
- 1998: ECP in acute GvHD
- 2008: ECP Rand. Study. cGvHD

Increasing use of ECP
Pilot Study of ECP in Acute Steroid-Refractory GvHD

- To evaluate the safety and efficacy of ECP.
- In addition to CSA and steroids at 2 mg/kg ECP performed on 2 consecutive days at 1 to 2 week intervals until improvement, then every 2 to 4 weeks until maximal response.
ECP in acute GvHD

- **Inclusion criteria**
  - Grades II to IV
  - Steroid-refractory (steroids at 2mg/kg b.w. for at least 4 days)
  - Steroid-dependent (flare-up during taper)
  - Karnofsky $\geq 50$
  - Signed written informed consent

- **Exclusion criteria**
  - Uncontrolled infection
  - ANC < 1.0 X 10⁹/l
  - Plts < 20 X 10⁹/l
  - Hemodynamic instability
  - Hypersens. to 8-MOP
  - Poor compliance
Intensified ECP in Acute Steroid - Refractory/Dependent GvHD Phase II Study

- **ECP started earlier** (steroids at 2mg/kg b.w. for at least 4 days or flare-up during steroid taper)
- Grades II to IV
- **ECP on 2 consecutive days per week**
- No maintenance ECP

Greinix et al, Haematologica 2006
# Comparison Pilot Study and Phase II Study

<table>
<thead>
<tr>
<th></th>
<th>All N=59</th>
<th>Pilot N=21</th>
<th>Phase II N=38</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>II/III/IV at ECP</strong></td>
<td>36/13/10</td>
<td>10/6/5</td>
<td>26/7/5</td>
</tr>
<tr>
<td><strong>Skin alone</strong></td>
<td>31</td>
<td>8</td>
<td>23*</td>
</tr>
<tr>
<td><strong>Skin+liver</strong></td>
<td>13</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td><strong>Skin+liver+gut</strong></td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>7</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td><strong>HCT-ECP d</strong></td>
<td>37 (17-70)</td>
<td>41 (20-70)</td>
<td>36 (17-69)*</td>
</tr>
<tr>
<td><strong>D steroids prior ECP</strong></td>
<td>17 (4-49)</td>
<td>21 (9-49)</td>
<td>16 (4-43)*</td>
</tr>
<tr>
<td><strong>Cum. steroid dose first-line mg/kg</strong></td>
<td>2.8 (2-10.4)</td>
<td>3.9 (2-10.4)</td>
<td>2.1 (2-6.5)*</td>
</tr>
<tr>
<td><strong>Med. steroids at start of ECP mg/kg</strong></td>
<td>2.1 (0.7-10.4)</td>
<td>2.6 (1.1-10.4)</td>
<td>1.9 (0.7-2.3)*</td>
</tr>
</tbody>
</table>

Greinix et al, Haematologica 2006
ECP as Second-line Therapy in Acute Steroid-Refractory and Steroid-Dependent GvHD

Greinix et al, Haematologica 2006
ECP as Second-line Therapy in Acute Steroid-Refractory and Steroid-Dependent GvHD

Greinix et al, Haematologica 2006
Acute Steroid-Refractory and Steroid-Dependent GvHD

**Results of ECP**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Pilot</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ECP cycles</td>
<td>7 (1-45)</td>
<td>11 (1-45)</td>
<td>5 (1-16)</td>
</tr>
<tr>
<td>Length ECP mo</td>
<td>3 (0.5-31)</td>
<td>5 (1-31)</td>
<td>1.5 (0.5-7)</td>
</tr>
<tr>
<td>Max. response after ECP cycle</td>
<td>4 (1-13)</td>
<td>4 (1-13)</td>
<td>4 (1-8)</td>
</tr>
<tr>
<td>Max. response after months</td>
<td>1.3 (0.5-6)</td>
<td>2 (0.5-6)</td>
<td>1.2 (0.5-4.5)</td>
</tr>
<tr>
<td>DC steroids d</td>
<td>55 (17-284)</td>
<td>53 (18-122)</td>
<td>56 (17-284)</td>
</tr>
<tr>
<td>Steroid dose 4 weeks after start</td>
<td>0.9 (0-5) mg/kg</td>
<td>1.1 (0-5) mg/kg</td>
<td>0.7 (0-2) mg/kg</td>
</tr>
<tr>
<td>Steroid dose 8 weeks after start</td>
<td>0.3 (0-1.5)mg/kg</td>
<td>0.3 (0-1.3)mg/kg</td>
<td>0.2 (0-1.5)mg/kg</td>
</tr>
</tbody>
</table>

Greinix et al, Haematologica 2006
TRM of Patients with Steroid-Refractory Acute GvHD According to Response to Second-Line ECP

Hazard Ratios for TRM

- Female gender
- Higher grade of GVHD during first-line
- Higher grade of GVHD at start of ECP
- More organs involved during first-line
- More organs involved at start of ECP
- Shorter interval from D0 to start of ECP
- Time to start of steroids
- Days of steroids prior ECP
- Higher cum. steroid dose first-line
- Higher steroid dose at start of ECP
- Lower number of ECP given
- Shorter duration of ECP
- Steroids < 1 mg/kg b.w. 4 weeks after start of ECP
- Steroids < 0.5 mg/kg b.w. 8 weeks after start of ECP
- No CR 3 months after start of ECP

Greinix et al, Haematologica 2006
Overall Survival of Patients with Steroid-Refractory Acute GvHD According to Best Response to Second-Line ECP

**Probability in %**

- CR to ECP
- PR to ECP
- NC
- NR

**Hazard Ratios for Overall Survival**

- Female gender
- Higher grade of GVHD during first-line
- Higher grade of GVHD at start of ECP
- More organs involved during first-line
- More organs involved at start of ECP
- Shorter interval from D0 to start of ECP
- Time to start of steroids
- Days of steroids prior ECP
- Higher cum. steroid dose first-line
- Higher steroid dose at start of ECP
- Lower number of ECP given
- Shorter duration of ECP
- Steroids < 1 mg/kg b.w. 4 weeks after start of ECP
- Steroids < 0.5 mg/kg b.w. 8 weeks after start of ECP
- No CR 3 months after start of ECP

**Greinix et al, Haematologica 2006**
### Acute Steroid-Refractory/Dependent GvHD

**Outcome after ECP (n=96)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>52 (54)</td>
</tr>
<tr>
<td>No chronic GVHD</td>
<td>36/52 (69)</td>
</tr>
<tr>
<td>Relapse</td>
<td>17 (18)</td>
</tr>
<tr>
<td>Med. FU yrs</td>
<td>6 (0.5-15)</td>
</tr>
</tbody>
</table>
ECP in Steroid-refractory Acute GvHD

Long-Term Results (n=96)
ECP in Steroid-refractory Acute GvHD
Long-Term Survival according to Response (n=96)

- CR to ECP: p<0.0001
Second-Line ECP in Acute Steroid-Refractory GvHD

- ECP is effective and well-tolerated adjunct second-line therapy.
- **Start ECP early** for ↑ CR and ↓ TRM.
- **Apply ECP weekly** on 2-3 days.
- Short ECP treatment times, no flare-ups.
- **Rapid steroid taper**: ↓ TRM and ↑ OS.
- GvL not affected.
Efficacy of ECP is not a result of generalized immunosuppression

- No increase of opportunistic infections or relapse during ECP
- No suppression of T- or B-cell responses to novel or recall antigens after ECP

Suchin et al, J Am Acad Dermatol 1999

Improvement in immune reconstitution after ECP in experimental allo BMT

Gatza et al, Blood 2008
ECP in Steroid-refractory Acute GvHD
Long-Term Results on Relapse (n=96)

CR to ECP
PR to ECP
no response to ECP

p=0.42
Safety

- **Excellent safety profile**
- **Reported adverse events**
  - Hypotension in 2-4%
  - Dizziness in up to 4%
  - Chills in up to 5%
  - Anemia
- **Catheter-related side effects**
  - CVC-related infections
  - Venous thrombosis
## ECP in Steroid-Refractory Acute GvHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts</th>
<th>CR/PR Skin %</th>
<th>CR/PR Liver %</th>
<th>CR/PR Gut %</th>
<th>OS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvaneschi 01</td>
<td>9</td>
<td>89</td>
<td>20</td>
<td>60</td>
<td>67</td>
</tr>
<tr>
<td>Dall‘Amico 02</td>
<td>14</td>
<td>79</td>
<td>57</td>
<td>70</td>
<td>57</td>
</tr>
<tr>
<td>Messina 03</td>
<td>33</td>
<td>82</td>
<td>60</td>
<td>75</td>
<td>69</td>
</tr>
<tr>
<td>Kanold 07</td>
<td>12</td>
<td>100</td>
<td>67</td>
<td>83</td>
<td>75</td>
</tr>
<tr>
<td>Greinix 06</td>
<td>59</td>
<td>93</td>
<td>65</td>
<td>74</td>
<td>47</td>
</tr>
<tr>
<td>Calore 08</td>
<td>15</td>
<td>92</td>
<td>100</td>
<td>71</td>
<td>85</td>
</tr>
<tr>
<td>Perfetti 08</td>
<td>23</td>
<td>66</td>
<td>27</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td>Perotti 10</td>
<td>50</td>
<td>83</td>
<td>67</td>
<td>73</td>
<td>64</td>
</tr>
</tbody>
</table>
ECP in Steroid-Refractory Acute GvHD

297 pts reported in 24 publications.

CR/PR Skin  75%  (50-100%)
CR/PR Liver  47%  (0-100%)
CR/PR Gut    58%  (0-100%)
OS           60%  (37.5-85%)

ECP is effective and well-tolerated adjunct second-line therapy.
ECP vs Anticytokine Therapy

- **Retrospective comparison** of patients with aGvHD given second-line treatment
  - Steroid-Refractory: progression after 3 d or no response after 7 d
  - Steroid-Dependent: recurrence during taper

- **Patient selection criteria**
  - HCT after January 2005
  - ≥ grade 2
  - Steroids ≥ 1 mg/kg/day alone as first-line therapy

- **Continuation of CNIs during second-line therapy**

- **Comparison of extracorporeal photopheresis with anticytokines**
  - **Inolimomab** (anti-IL2R): 0.3 mg/kg/d x 8 d, 0.4 mg/kg x 3/w for 3 w
  - **Etanercept** (anti-TNR): 25 mg x 2/w for 4 w, 25 mg/w for 4 w
  - **ECP**: 2-3 d/week

### Patient and Transplant Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics N (%) ( n=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Center</strong></td>
</tr>
<tr>
<td>Vanderbilt</td>
</tr>
<tr>
<td>[ ]</td>
</tr>
<tr>
<td>Nottingham</td>
</tr>
<tr>
<td>Vienna</td>
</tr>
<tr>
<td>Paris</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Age (y) (median)</strong></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td>Acute Leukemia</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Myeloid Disorders</td>
</tr>
<tr>
<td>Myeloma</td>
</tr>
</tbody>
</table>
Response to ECP (n=86)

Response to Anticytokine Therapy (n=41)
## Overall Response to 2nd Line Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>ECP N (%)</th>
<th>Non-ECP N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response*</td>
<td>62 (73%)</td>
<td>13 (32%)</td>
</tr>
<tr>
<td>PR</td>
<td>9 (11%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>CR**</td>
<td>53 (62%)</td>
<td>8 (20%)</td>
</tr>
</tbody>
</table>

* P<0.0001

** P<0.001

Survival and NRM: ECP vs. Non-ECP

Inclusion of ECP in Acute GvHD Treatment Guidelines
Frequency of Treatments Evaluated in Literature Review of ASBMT

Martin PJ et al, BBMT 2012; 18:1150-63
ASBMT Recommendations
ECP for Second-line Therapy

• **Toxicity concerns**
  Limited, blood loss from the extracorporeal circuit, hypocalcemia due to anticoagulant, mild cytopenia, catheter-associated bacteremia but on increased risk of overall infections

• **Significant interactions:** None

• **Viral reactivation concerns:** Not increased

• **Schedule**
  3 in week 1, 2 per week weeks 2-12 and 2 per 4 weeks thereafter.

Martin PJ et al, BBMT 2012; 18:1150-63
<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicity</th>
<th>Sig. interactions</th>
<th>Viral reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP</td>
<td>Limited</td>
<td>None</td>
<td>Not increased</td>
</tr>
<tr>
<td>Steroids</td>
<td>High</td>
<td>None</td>
<td>High</td>
</tr>
<tr>
<td>MMF</td>
<td>Cytopenia, GI</td>
<td>Myelosuppress.</td>
<td>Moderately high</td>
</tr>
<tr>
<td>Denileukin Diftitox</td>
<td>↑ hepatic transam.</td>
<td>None</td>
<td>High</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Cytopenia, HUS/TAM</td>
<td>CYP3A or P-glyc.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Infliximab</td>
<td>None</td>
<td>None</td>
<td>Very high</td>
</tr>
<tr>
<td>Etanercept</td>
<td>None</td>
<td>None</td>
<td>High</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>Myelosupress., liver, renal</td>
<td>None</td>
<td>Very high</td>
</tr>
<tr>
<td>Horse ATG</td>
<td>Anaphylaxis, cytopenia</td>
<td>None</td>
<td>Very high</td>
</tr>
<tr>
<td>Rabbit ATG</td>
<td>Cytopenia, infections</td>
<td>None</td>
<td>Very high</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Pancytopenia, infusion-AE</td>
<td>None</td>
<td>Very high</td>
</tr>
</tbody>
</table>

Martin PJ et al, BBMT 2012; 18:1150-63
BCSH and BSBMT Recommendations on Second-Line Therapy of Acute GvHD

• The following agents are suggested:
  – ECP
  – Anti-TNFα antibodies
  – mTOR inhibitors
  – MMF
  – IL-2R antibodies

• Level of evidence: 2C (suggest, current evidence from observational studies, case series)

Dignan FI et al, BJH 2012;158:30-45
SIdEM and GITMO Recommendations on Use of ECP in Acute GvHD

- ECP is a valuable option for acute GvHD not responding to steroids and CNI.
- ECP may be used in adults and children.
- Early start of ECP is indicated particularly in children and recipients of haploidentical or unrelated donor HCT.

Pierelli L et al, Transfusion accepted Nov 2, 2012
ECP and Mechanisms of Action 2013

1. Methoxalen + UVA radiation
   - Cross-linked DNA

2. Phagocytosis

3. Apoptosis

4. Tolerogenic DC/APC
   - BAFF
   - Anti-inflammatory cytokines (e.g., IL-10, TGF-β)

5. Treg
   - Pro-inflammatory cytokines (e.g., IL-12, IFNγ)
   - Stimulation T-effector cells

- Receptor-mediated signaling
- Anti-inflammatory cytokines (e.g., IL-10, TGF-β)

- Treg
ECP for Treatment of GvHD

• **Chronic GvHD**
  – Established second-line therapy worldwide
  – High response rates in cutaneous and extracutaneous GvHD manifestations
  – Steroid-sparing effect, no main side effects
  – Improved quality of life and OS
  – No negative effect on GvL
  – Investigation of ECP upfront ongoing

• **Acute GvHD**
  – Accepted salvage therapy of steroid-refractory disease
  – Investigation of ECP upfront ongoing
GvHD Study Group Vienna

BMT Unit
- P. Kalhs
- W. Rabitsch
- Z. Kuzmina
- A. Schulenburg
- C. Zielinski

Dept. Immunology
- W. F. Pickl

Dept. Dermatology
- R. Knobler
- U. Just
- A. Tanew
- G. Bauer

Dept. Transfusion Medicine
- N. Worel
- G. Leitner

Dept. Gastroenterology
- J. Hammer

Dept. Pulmonology
- V. Petkov
ECP Reduces GvHD and Mortality in Minor-MM Mouse Model

Gatza et al, Blood 2008

*\(p<0.004\) vs L-15

\(*p=0.0007\) vs L-15
Infusion of ECP-treated Splenocytes Increases Donor Treg after Allo BMT

Gatza et al, Blood 2008
Salvage ECP in Acute Steroid-Refractory GvHD

Rapid Steroid Reduction during ECP

Perfetti et al, BMT 2008

Perotti et al, Transfusion 2010

## ECP in Steroid-Refractory Acute GvHD

### Adverse Events*

<table>
<thead>
<tr>
<th>Event</th>
<th>No pts (%)</th>
<th>No episodes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Hb $&gt;1\text{g/dL}$</td>
<td>19 (90)</td>
<td>74 (16)</td>
</tr>
<tr>
<td>Renewed RBC Tf</td>
<td>10 (48)</td>
<td>26 (6)</td>
</tr>
<tr>
<td>↓ ANC $&lt;1.5 \times 10^9/L$</td>
<td>17 (81)</td>
<td>40 (9)</td>
</tr>
<tr>
<td>↓ ANC $&lt;1 \times 10^9/L$</td>
<td>7 (33)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>↓ ANC $&lt;0.5 \times 10^9/L$</td>
<td>5 (24)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>↓ Plts $&gt;50%$</td>
<td>15 (71)</td>
<td>75 (16)</td>
</tr>
<tr>
<td>↓ Plts $&lt;20 \times 10^9/L$</td>
<td>5 (24)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Renewed Plts Tf</td>
<td>7 (33)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3 (14)</td>
<td>3 (0.6)</td>
</tr>
</tbody>
</table>

*21 pts, 460 procedures

Blood 2000;96:2426-2431
ECP in Steroid-Refractory Acute GvHD

Publications (n=24)

Published Patients (n=297)