Extracorporeal photopheresis in graft-versus-host disease.
Eight years of experience in children and adults in Wroclaw.

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23 - 24 October 2014, Warsaw, Poland
Extracorporeal photopheresis

The problem with GVHD
Salvage therapy in resistant aGVHD

- Steroids
- Purine synthesis inhibitors: MMF
- ATG

- Phototherapy
  - ECP
  - PUVA

- MoAb:
  - Etanercept
  - Basiliximab
  - [US: Daclizumab]
  - Alemtuzumab
  - Tocilizumab

- Mesenchymal stem cells (MSC)
- mTOR inhibitors: Sirolimus
- CNI: Tacrolimus
- Pentostatin
Salvage therapy in resistant cGVHD

- Pulse of steroids
- CNI: CSA, tacrolimus
- Purine synthesis inhibitors: Azathioprine, MMF

**Phototherapy**
- ECP
- PUVA

- MoAb:
  - Rituximab
  - Etanercept
  - Alemtuzumab

- mTOR inhibitors: sirolimus
- Thalidomide
- Methotrexate
- Pentostatin
- Imatinib
Extracorporeal photopheresis

Selected technical facts
ECP, Therakos UVAR XTS
ECP, Therakos CELLEX
Comparison of in-line methods

**UVAR XTS**
- Quieter
- Longer treatment
- Single-needle only
- Latex ports

**CELLEX**
- Shorter procedures
- Continuous flow system (single- and double needle)
- No latex
- Blood priming available!
  - Low BW
  - Low HGB
  - Less vasovagal episodes
ECP off-line technique
Clinical background

Extracorporeal photopheresis
• Steroid-resistant GVHD
  – aGVHD
    • Progression after 4 days of steroid therapy
    • Non-response after 7 days of steroid therapy
    • Partial response after 14 days of steroid therapy
  – cGVHD
    • Progression after 2 weeks of therapy
    • Non-response after 1 month of therapy
    • Partial response after 2 months of therapy
• Steroid-dependent GVHD
  – Methylprednisolone dose over 0.5 mg/kg/day
• Intolerance or complications of steroid therapy
Contraindications

- Active malignancy requiring chemotherapy
- Severe infection
- Hemodynamically unstable patient
- WBC<1 K/uL
- PLT<20 K/uL
- 8-MOP hypersensitivity
- Aphakia
ECP schedule in aGVHD

weeks

1

2

3

4

Clinical effect
ECP schedule in cGVHD

weeks: 0 4 8 12 16 20 24 28

Clinical effect
Extracorporeal photopheresis

When does it work?
ECP in aGVHD

11 studies, 293 patients

Pierelli et al., Transfusion 2013

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Number</th>
<th>Age (year)</th>
<th>Skin N</th>
<th>Skin R</th>
<th>Liver N</th>
<th>Liver R</th>
<th>Gastrointestinal N</th>
<th>Gastrointestinal R</th>
<th>Overall response</th>
<th>Survival (%)</th>
<th>Steroid Reduction or stop</th>
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<td>40</td>
<td>22 &gt;13</td>
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<td>21-60</td>
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<td>&gt;47</td>
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<td>&gt;14</td>
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<td>Berger</td>
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<td>6</td>
<td>CR 9; NR 6</td>
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<td>6</td>
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<td>CR 7; PR 3; NR 2;</td>
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<td>CR 16; PR 18</td>
<td>44</td>
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<td>24</td>
<td>11</td>
<td>8</td>
<td>8 stopped, 25 tapered</td>
<td>44</td>
<td>Stopped after 17-284 days</td>
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</tbody>
</table>

* Empty cells: no data reported in the paper.
† Including patients with both skin and other organ GVHD.
CR = complete response; N = number of assessed patients; NR = no response; PR = partial response; R = number of responders.

- 5-fold drop in mortality in ECP responders
- BUT: in MVA the strongest predictor for response was aGVHD severity
  
  **G2: 100% vs G3-4: 30%**
ECP in cGVHD
22 studies, 633 patients

Pierelli et al., Transfusion 2013

Steroid tapering 34%
Steroid discontinuation at 1Y – 22%

23 – 24 October 2014, Warsaw, Poland

<table>
<thead>
<tr>
<th>Agent</th>
<th>Recommendation</th>
<th>Evidence</th>
<th>Side Effects</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Steroids</td>
<td>B</td>
<td>III-I</td>
<td>osteoporosis, avascular necrosis, diabetes</td>
<td>important but need to spare steroids because of side effect profile</td>
</tr>
<tr>
<td>Photopheresis</td>
<td>C-1</td>
<td>II</td>
<td>venous access required</td>
<td>spares steroids, excellent safety profile</td>
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<tr>
<td>mTOR inhibitors</td>
<td>C-1</td>
<td>III-I</td>
<td>TAM, hyperlipidemia, hematotoxicity</td>
<td>increased risk for TAM in combination with CNI, lower efficacy in thrombocytopenia, requires frequent monitoring</td>
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<tr>
<td>CNI</td>
<td>C-1</td>
<td>III-I</td>
<td>renal toxicity, hypertension</td>
<td>spares steroids, should be avoided in renal impairment</td>
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<tr>
<td>MMF</td>
<td>C-1</td>
<td>III-I</td>
<td>GI complaints, infectious and relapse risk</td>
<td>increased risk for viral reactivation, spares steroids, GI toxicity may mimic GVHD clinically and histologically</td>
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<tr>
<td>Pentostatin</td>
<td>C-2</td>
<td>II</td>
<td>Hematotoxicity, infectious risk</td>
<td>best results in children, caution in presence of impaired marrow function, long-term immunosuppression</td>
</tr>
<tr>
<td>MTX</td>
<td>C-2</td>
<td>III-I</td>
<td>Hematotoxicity</td>
<td>best response in mucocutaneous cGVHD, spares steroids</td>
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<tr>
<td>Imatinib</td>
<td>C-2</td>
<td>III-I</td>
<td>Fluid retention</td>
<td>best results in sclerotic skin lesions, potentially effective in mild and moderate BO</td>
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<tr>
<td>Rituximab</td>
<td>C-2</td>
<td>II</td>
<td>Infectious risk</td>
<td>effective in auto-antibody mediated manifestations as well as cutaneous and musculoskeletal cGVHD</td>
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<tr>
<td>Hydroxychloroquine</td>
<td>C-2</td>
<td>III-2</td>
<td>GI complaints</td>
<td>best results in mucocutaneous and liver involvement</td>
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<td>Clofazimine</td>
<td>C-2</td>
<td>III-2</td>
<td>GI complaints, skin hyperpigmentation</td>
<td>best results in mucocutaneous cGVHD</td>
</tr>
<tr>
<td>Thoracoabdominal irradiation</td>
<td>C-2</td>
<td>III-2</td>
<td>Hematotoxicity</td>
<td>best results in fasciitis or steroid dependent mucocutaneous cGVHD, caution in presence of impaired marrow function</td>
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<tr>
<td>Pulse of steroids</td>
<td>C-2</td>
<td>III-2</td>
<td>Infectious risk</td>
<td>rapid control of symptoms, identification of steroid resistance</td>
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<td>Thalidomide</td>
<td>C-3</td>
<td>II</td>
<td>Neurotoxicity, sedation, constipation</td>
<td>may be used in concomitant relapse of MM</td>
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<td>Azathioprine</td>
<td>C-3</td>
<td>III-1</td>
<td>Hematotoxicity, infectious risk</td>
<td>increased risk for oral malignancies</td>
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<td>Retinoids</td>
<td>C-3</td>
<td>III-2</td>
<td>Skin toxicity, hyperlipidemia</td>
<td>effective in sclerotic skin lesions</td>
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<td>Alemtuzumab</td>
<td>C-4</td>
<td>III-3</td>
<td>Infectious risk</td>
<td>last resort</td>
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<tr>
<td>Alefacept</td>
<td>C-4</td>
<td>III-3</td>
<td>Infectious risk</td>
<td>last resort</td>
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<tr>
<td>Etenaccept</td>
<td>C-4</td>
<td>III-3</td>
<td>Infectious risk</td>
<td>may be used in overlap syndrome with GI manifestations</td>
</tr>
</tbody>
</table>

TAM indicates transplantation-associated microangiopathy; CIN, calcineurin inhibitor; cGVHD, chronic graft-versus-host disease; BO, bronchiolitis obliterans.
Extracorporeal photopheresis

Wrocław experience
ECP in Wrocław

- 8 years, 1025 procedures
  - UVAR XTS – 920
  - CELLEX – 92
  - „Three-step” - OPTIA/UVAR XTS – 13
- 52 patients, age 3.7- 59 (median 19 years)
  - aGVHD - 18
  - cGVHD - 34
- 26 – Port-a-Caths
ECP in aGVHD

16 patients

Y

RESPONSE

N

8 pts

5/8 alive&well

8 pts

0/8 alive
pSU after ECP in GVHD patients with a/cGVHD
UV-Irradiated leukocyte counts in ECP
M.P., ALL 2CR MUD-PBSCT, aGVHD IV

Daily stool volume

- ECP
- BASILIXIMAB
- ETANERCEPT

CSA
GCS
MMF

MSC
ECP in cGVHD

34 patients

Y

RESPONSE

N

18 pts

9 pts

7/7 alive

7 patients

16/18 alive

4/9 alive
cGVHD: pSU in ECP responders vs non-responders

p=0.07

Responders, 5yr pSU=0.88
Others, 5yr pSU=0.50
P.P., ALL 2CR, MSD, cGVHD
Prednisone reduction after ECP

Ussowicz M et al. Transplant Proc 2013
16 patients
- aGVHD – 13 (9 responses)
- cGVHD – 3 (1 response)
460 procedures

Progress in the ECP field
„MINIPHOTOPHERESIS“

Method
- 100-200 mL blood drawn with cord blood collection system - MQT2205PU
- Buffy coat separation - Compomatat G4
- 8-MOP
- UV Irradiation in BS05 UV Chamber (Gröbel)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Body weight (kg)</th>
<th>Grade</th>
<th>GVHD prophylaxis</th>
<th>Steroids before ECP</th>
<th>Onset GVHD</th>
<th>Start mini-ECP</th>
<th>Number of mini-ECP treatments</th>
<th>GVHD organs and grading*</th>
<th>Response</th>
<th>Current status</th>
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<tr>
<td>1</td>
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<td>ATG, CsA, MTX</td>
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<td>D18</td>
<td>D18</td>
<td>18</td>
<td>Skin 3</td>
<td>PR</td>
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<td>2</td>
<td>15</td>
<td>II</td>
<td>CsA</td>
<td>Yes (steroid-refractory)</td>
<td>D31</td>
<td>D31</td>
<td>23</td>
<td>Skin 3</td>
<td>CR</td>
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<td>3</td>
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<td>TCD, Okt3</td>
<td>Yes (steroid-refractory)</td>
<td>D32</td>
<td>D32</td>
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<td>Skin 3</td>
<td>CR</td>
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<td>Yes (steroid-refractory)</td>
<td>D42</td>
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<td>Skin 3</td>
<td>CR</td>
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</table>

* Grading of acute GVHD according to Rowlings et al. 2009:

1: Caused by relapse of malignant disease.
2: Caused by rejection of transplanted organ.
3: Caused by viral infection (primary HSV infection).
4: Caused by rejection of transplanted organ.
5: Caused by rejection of transplanted organ.

References:
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