Acute GVHD

ESH-EBMT 2009
Latimer
A. Devergie
Acute GVHD

- Activated Donor T cells damage host epithelial cells after an inflammatory cascade that begins after the preparative regimen
- **GVHD is the major barrier to successful HSCT**
Risk factors

Donor
- Related/unrelated
- HLA mismatched
- Sex mismatched
- Alloimmunisation
- Source of stem cells

Recipient
- Age
- Conditioning regimen
- Prevention of GVHD

Incidence 10 to 80% (median ~ 40%)
## aGVHD: a 3-step process

<table>
<thead>
<tr>
<th>phase</th>
<th>cells</th>
<th>cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 conditioning</td>
<td>Host APC Epith cell</td>
<td>TNFα, IL1</td>
</tr>
<tr>
<td>2 T-cell activation</td>
<td>Donor T-cells</td>
<td>IL2, IFNγ</td>
</tr>
<tr>
<td>3 Effector phase</td>
<td>CTLs, NK</td>
<td>TNFα, IL1 Cytokine storm</td>
</tr>
</tbody>
</table>
Classical targets of aGVHD

Epithelial cells of

- **SKIN**: keratinocytes
- **LIVER**: biliary ducts
- **DIGESTIVE TRACT**: enterocytes

« satellite cell necrosis »
(infiltrating immune cell + apoptotic cell)
Gastro-intestinal involvement

- Anorexia, nausea
- Green watery diarrhoea
- Abdominal pain, bloody diarrhoea

Gastro-duodenal biopsies
Liver involvement

Cholestatic hepatopathy...

(other causes of hepatopathy: toxicity, infection, VOD...)

Other symptoms
Fever, eosinophilia .....
Staging of aGVHD

<table>
<thead>
<tr>
<th>stage</th>
<th>skin</th>
<th>Liver (bil:μmol/l)</th>
<th>Gut diarrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;25%</td>
<td>34-50</td>
<td>&gt;500 ml</td>
</tr>
<tr>
<td>2</td>
<td>25-50%</td>
<td>51-102</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>3</td>
<td>&gt;50%</td>
<td>103-255</td>
<td>&gt;1500</td>
</tr>
<tr>
<td>4</td>
<td>Lyell</td>
<td>&gt;255</td>
<td>pain++</td>
</tr>
</tbody>
</table>
**aGVHD grading (I – IV or A-D)**

<table>
<thead>
<tr>
<th>grade</th>
<th>skin</th>
<th>liver</th>
<th>gut</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1-2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>3, or</td>
<td>1, or</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>0-3</td>
<td>2-3, or</td>
<td>2-4</td>
</tr>
<tr>
<td>IV</td>
<td>4, or</td>
<td>4</td>
<td>0-4</td>
</tr>
</tbody>
</table>
Prognosis of aGVHD

Figure 1. Probability of survival according to maximum GVHD score. (A) IBMTR grade. (B) Glucksberg grade.

Cahn JY et al Blood 2005
Questions

• Can GVHD be prevented? (without an increase of relapse risk)
• What is the best 1st line therapy?
• Is it possible to predict the response to therapy and to avoid evolution to higher grades of aGVHD?
• What about 2nd line treatments?
• Can we improve immune reconstitution?
# Prevention and treatment of acute GVHD

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Primary Tt</th>
<th>Secondary Tt</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA + MTX</td>
<td>MethylPDN</td>
<td>High dose methyl PDN</td>
</tr>
<tr>
<td>TCD</td>
<td>2 mg/kg</td>
<td>ATG/MoAb</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>MMF</td>
<td></td>
<td>MMF</td>
</tr>
<tr>
<td>MethylPDN</td>
<td></td>
<td>Pentostatin</td>
</tr>
<tr>
<td>Sirolimus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prophylaxis of GVHD

Target: the 3 phases of aGVHD?

• **Conditioning therapy activates host tissues**: reduced intensity conditioning regimen??

• **Donor T cell response**: depletion or inactivation of donor T cells +++

• **Effector stage**? To block cytokines???
  (mainly used in Tt rather than in prophylaxis)
Prophylaxis of GVHD with CsA + MTX

« Gold standard » protocol since 1986
Cyclosporine 3 mg/kg/d d-1 to d+30 then orally until d+180
Methotrexate 15 mg/m² D+1, 10 mg/m² d+3, 6, ± 11

Both agents inhibit activated donor T cell proliferation
CsA + MTX ± Pred
Several trials

- Delay in onset of aGVHD
- Significant reduction of aGVHD? *
- Increased risk of infections: No
- Increased risk of relapse: No
- **Impact on overall survival: No**

Ruutu et al. Blood 2000 *
Storb et al Blood 2000
CsA-MTX / CsA-MTX-Pred

Hoyt et al BMT 2008

Figure 1  Cumulative incidence of GVHD requiring an increase in or addition of systemic immunosuppression to 180 days post transplant in patients receiving or not receiving prednisolone prophylaxis.
Prophylaxis of GVHD
T cell depletion of the graft

- *In vitro* T cell depletion (TCD) or positive selection of CD34+ stem cells with possible delayed T cell add-back
- *In vivo* TCD with ATG or MoAb

So far, it has not been conclusively established whether TCD can improve LFS
T-cell depletion trial
JE Wagner et al Lancet 2005

• 1995-2000: Malignant diseases, UD (2/3 HLA-A-B low resolution DRBI high resolution matched; 1/3 mismatched)
• 201 TCD arm / 204 CsA + MTX
• 3y DFS: 27% (TCD) 34% (C+M) p=0.16
• aGVHD: 18% (TCD) 37% (C+M) p<0.0001
• Relapse (CML): 20% (TCD) 7% (C+M) p=0.009
• CMV:28%/17% Aspergillosis:16%/7%
T-cell depletion in geno-id SCT
Jakubowski et al Blood 2007 (MSKCC)

• 52 adult patients, malignant diseases
• HFTBI, thiotepa, fluda. PBSC.
• aGVHD (grade II) 8%
• Cause of death (19): relapse (8), infection (8) GVHD (2) other (1)
• 3 y DFS: 61%
GITMO Randomized ATG trial; Blood 2001; 98:2942

Long term Follow up BBMT; 2006; 12: 560
Figure 1  Cumulative incidence of non-relapse mortality in patients treated with or without Thymoglobulin during conditioning before transplantation.
Figure 5  Probability of disease-free survival in patients treated with or without Thymoglobulin during conditioning before transplantation.
ATG for prevention of GVHD (155 AML UD)
Basara N for the German study group BMT 2005

Figure 4  LFS.
Phase III European multicenter trial of prophylaxis with CsA + MTX + ATG Fressenius
Finke J et al Preliminary results (2009)

• 201 patients randomized 2003-2007
• ATG: decreased incidence of aGVHD grade II-IV 33% vs 50% p=0.01, and of cGVHD 30.8% vs 58.8% p<0.001
• No difference in 2yDFS (51.6 vs 47.5), 2y TRM (19.6 vs 28.9), 2y relapse rate (28.9 vs 23.6)

In conclusion, reduction of occurrence of GVHD without compromising survival
Flu+Mel in AML and MDS: Alemtuzumab reduces aGVHD and cGVHD
Besien KV et al BBMT 2009

• 95 pts (F+M+Al.) compared to 59 pts (F+M).
• Grade II-IV aGVHD (RR: 5.5) and cGVHD (RR 6.6) lower with Al. (p<0.01)
• No differences in TRM, relapse, survival and DFS
Prior Rituximab: less aGVHD and better survival after alloPBSCT?
Ratanatharathorn et al Br J haematol 2009

- Prior Tt with RTX might attenuate AG presentation by B-cells
- 435 pts transplanted (1999-2004) for B-cell Lymphoma
- 179 received RTX within 6m prior to transplant., 256 did not
- RTX cohort: lower TRM (RR=0.68), lower aGVHD (RR=0.72), better PFS (RR=0.68) abd OS (RR=0.63)
Tacrolimus

- As CsA, it inhibits T-cell activation and IL2 production (calcineurin inhibitor)
- Nephrotoxicity++
- Several randomized trials comparing CsA + MTX to T + MTX have been conducted in patients transplanted with id sib donors or matched unrelated donors
Tacrolimus instead of CSA for prophylaxis of GVHD

• Rathanatharathom et al. Blood 1998 (multicenter trial) 329 patients (id sib donor)
• Nash et al Blood 2000 (multicenter trial) 180 patients (MUD)
• Yanada et al. 2004 BMT (retrospective study) 1935 patients (id sib) and 777 patients (MUD)
T + MTX / CsA + MTX

Overall results of trials

• Diminution of grade II-IV AGVHD
• + increase of toxicity
• + increase of relapse
• Overall survival: idem, or decreased (advanced disease) or increased
1935 id sib and 777 UD HSCT in Japan
Yanada M et al BMT 2004
Phase III trial CsA + MTX / Tacro + MTX
Ratanatharathorn et al Blood 1998

Fig 4. Overall survivals at 2 years of 165 patients who received cyclosporine/methotrexate, 57.2% (●) and 164 patients who received tacrolimus/methotrexate 46.9% (□); absolute difference = 10.3%, 95% CI interval = −21.1 to 0.5 (P = .02, Wilcoxon).
Sirolimus

Macrolide IS used in solid organ Tx
3 clinical trials of S + T ± MTX (Cutler C, Antin JH. Bone Marrow Transplant 2004)
Results: Decreased incidence of grade II-IV GVHD but increased rates of thrombotic microangiopathy (TM)
Everolimus + T (Platzbecker U. BBMT 2009): TM + VOD ++ (54%)!
Cutler et al Blood 2007 (53 id sib + 30 UD)

Cumulative Incidence of Acute GVHD with Death as Competing Risk

tacrolimus + sirolimus
Overall Survival

Months from Transplantation

tacrolimus + sirolimus

URD, Combined, MRD
MMF

Antimetabolite: it blocks T- and B cell proliferation (myelotoxicity)
The efficacy of MMF + CsA has been studied mainly in RIC regimens

In « standard » SCT, CsA+MMF appears equivalent to CsA + MTX, with faster engraftment and decreased incidence of mucositis

Bolwell et al. BMT 2004
Neumann et al. BMT 2005
Nash et al BBMT 2005
Treatment of acute GVHD
1st line treatment

• « High dose » steroids 2 mg/kg: primary Tt for more than 25y
• Questions:
  Higher dose?
  Lower dose?
  1st line combination of steroid + other IS treatment?
95 patients with grade ≥ II AGVHD
Van Lint et al (GITMO) Blood 1998

Early treatment of aGVHD with high or low dose of 6MPred

Fig 1. Actuarial probability of TRM for patients randomized to receive 2 mg/kg of 6MPred (47 patients, 28%) (A), or 10 mg/kg (48 patients, 32%) (B). There is no significant difference ($P = .7$).
Prognostic value of the response to 2 mg/kg

Van Lint et al Blood 1998

Fig 2. Actuarial TRM for patients randomized to receive 2 mg/kg of 6MPred. Day-5 responders (A) are patients who continued with tapering doses of 6MPred on day 5 of therapy (n = 19; TRM = 16%). Day-5 nonresponders are patients who had the dose of 6MPred increased on day 5 because of nonresponse or progression of aGvHD (n = 25; TRM = 46%). The difference in TRM between day-5 responders and day-5 nonresponders is significant (P = .007).
1 versus 2 mg/kg?
Mielcarek et al (Blood 2009)

- Retrospective study of 733 patients with grade I-II aGVHD treated with « standard dose » (n=386) versus « low dose » (n=347)
- Similar rates of TRM, relapse, survival
- Low dose: 48% reduction of D100 cumulative prednisone dose, decreased incidence of invasive fungal infection
Figure 1. Time to CR for patients with GVHD treated with steroids alone or etanercept plus steroids. (A) Time to CR for all patients with GVHD treated with steroids alone (n = 99; dotted line) or etanercept plus steroids (n = 61; solid line). (B) Time to CR for patients who underwent related-donor HCT treated with steroids alone (n = 53) or with etanercept plus steroids (n = 42). (C) Time to CR for patients who underwent unrelated-donor HCT treated with steroids alone (n = 46) or with etanercept plus steroids (n = 19). The 95% confidence intervals for CR rate at 4 weeks are shown as error bars in panels A to C. Overall survival curves through 6 months from initiation of GVHD treatment by treatment group for all patients (D), patients who underwent related-donor HCT (E), and patients who underwent unrelated-donor HCT (F). The 95% confidence intervals for survival at 6 months are shown as error bars in panels D to F.
1st line Tt with Steroid + 1 other IS agent
Alousi A.M. et al BLOOD 2009

• 4 arm phase II trial in 180 patients (2005-2008): Steroid + MMF (45) or Etanercept (46) or Denileukin (47) or Pentostatin (42)

• CR was highest with MMF and OS at 9m post randomization was 64%, followed dy D (49%), E (47%) and P(47%)
MMF is the most promising agent to study in a phase III trial...

Figure 1a: Cumulative Incidence of CR by Treatment Arm

Figure 1b: Overall Survival 9 months Post Randomization by Treatment Arm
# 2nd line treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>response</th>
<th>survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG</td>
<td>51%</td>
<td>35%</td>
</tr>
<tr>
<td>AntiRIL2</td>
<td>40-70%</td>
<td>≤30%</td>
</tr>
<tr>
<td>AntiTNF</td>
<td>67%</td>
<td>38%</td>
</tr>
<tr>
<td>CsA to tacro</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Tacro + ATG</td>
<td></td>
<td>35%</td>
</tr>
<tr>
<td>MMF</td>
<td>40%</td>
<td>16% - 37%</td>
</tr>
<tr>
<td>pentostatin</td>
<td>50%</td>
<td>26%</td>
</tr>
<tr>
<td>OKT3</td>
<td>50%</td>
<td>45%</td>
</tr>
</tbody>
</table>
Conclusion

- Poor prognosis of steroid-refractory AGVHD
- Many IS agents are active…but predispose to infections+++
- Lack of uniform criteria of response to various therapies
- None of these Tt has been consistently successful in salvaging patients
- Initial control of AGVHD is critical
Supportive Care +++

- Intensified infection prophylaxis ++++ (viral, bacterial and mycotic infections are the most common causes of death in patients with severe aGVHD)
- Nutritional support, replacement therapy of enteral losses of fluids...
- Bone mineral retention and repair
- Pain control