Auto/Allo for DLBCL

Koen van Besien, MD
Weill Cornell Medical College, NY
Topics

- Autologous SCT: Current standards
  - Parma
  - Coral
  - Age
  - Salvage
  - Conditioning

- Auto in CR1
  - Historical
  - Double Hit Lymphoma

- Auto for Partial Response

- Allogeneic Transplantation
  - Controversial role
  - Improving access and outcomes.
Clinical factors at relapse influence outcome following autoSCT

- Chemorefractory disease
  - Pts achieving less than a PR?
  - Pts with PD?
- > 3 prior regimens
- Elevated LDH
- Time to relapse < 12 months
- High disease burden
- Bulky disease (> 10 cm)
- Prior Rituximab

Van Besien BMT 2001
Vose JCO 1993
Prince Br J Hem 1996
Guglielmi JCO 1998
Moskowitz BMT 1999
Coral Study

Gisselbrecht C et al. JCO 2010;28:4184-4190
Horwitz, Blood, 2004
Coral Study outcomes depending on prior rituximab and duration of initial remission

Prior Rituximab vs Not

Initial remission >= 12 mo

Prior rituximab and CR1<12 months

Gisselbrecht C et al. JCO 2010;28:4184-4190
Maintenance Rituximab after ASCT for DLBCL

Gisselbrecht C et al. JCO 2012
Topics

- Autologous SCT: Current standards
  - Parma
  - Coral
  - Age
  - Salvage
  - Conditioning

- Auto in CR1
  - Historical
  - Double Hit Lymphoma

- Auto for Partial Response

- Allogeneic Transplantation
  - Controversial role
  - Improving access and outcomes.
PFS after ASCT in older NHL

Full dose BEAM
N=73, m age 67 (65-74), **D100 TRM 3%**
*Martin et al, LL 2015, France*

BEAM 74%
N=202, m age 65 (60-74), **D100 TRM 4%**
*Dahi et al, BBMT 20, 2004, 2014, MSKCC*
Topics

- **Autologous SCT: Current standards**
  - Parma
  - Coral
  - Age
  - Salvage
  - Conditioning

- **Auto in CR1**
  - Historical
  - Double Hit Lymphoma

- **Auto for Partial Response**

- **Allogeneic Transplantation**
  - Controversial role
  - Improving access and outcomes.
Coral Study

Gisselbrecht C et al. JCO 2010;28:4184-4190
Thieblemont, JCO 2011
Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12

Crump et al, JCO 32, 3940, 2014
Topics

- **Autologous SCT: Current standards**
  - Parma
  - Coral
  - Age
  - Salvage
  - Conditioning

- **Auto in CR1**
  - Historical
  - Double Hit Lymphoma

- **Auto for Partial Response**

- **Allogeneic Transplantation**
  - Controversial role
  - Improving access and outcomes.
Conditioning Regimens

Risk for IPS

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBV$_{\sim 450}$</td>
<td>1.88</td>
<td>0.003</td>
</tr>
<tr>
<td>CBV$_{\sim 300}$</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>BuCy</td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td>TBI</td>
<td>2</td>
<td>0.002</td>
</tr>
</tbody>
</table>

R-BEAM is the standard
There is worse... not better

Chen et al, BBMT 2015
Phase III randomized study of RBEAM compared with iodine-131 tositumomab/BEAM psed diffuse large B-cell lymphoma: results from the BMT CTN 0401 trial

Vose JCO, 2013
Bendamustine EAM

Capria et al, Blood 124,3030, 2014
Topics

- **Autologous SCT: Current standards**
  - Parma
  - Coral
  - Age
  - Salvage
  - Conditioning

- **Auto in CR1**
  - Historical
  - Double Hit Lymphoma

- **Auto for Partial Response**

- **Allogeneic Transplantation**
  - Controversial role
  - Improving access and outcomes.
Topics

- **Autologous SCT: Current standards**
  - Parma
  - Coral
  - Age
  - Salvage
  - Conditioning

- **Auto in CR1**
  - Historical
  - Double Hit Lymphoma

- **Auto for Partial Response**

- **Allogeneic Transplantation**
  - Controversial role
  - Improving access and outcomes.
Allo vs auto BMT for lymphoma

Disease Free survival
Allograft (n=31) vs autograft (n=35)

Recurrence rate
Allograft (n=31) vs autograft (n=35)

Schimmer et al Bone Marrow Transplant. 26:859-64, 2000.
An Endangered Species
“The outcomes of allogeneic transplantation are horrible”

“As far as allogeneic transplantation is concerned, I am a nihilist”

“I send patients for two second opinions before recommending an allo transplant”
Why this bad reputation?

- Concern over TRM
- Concern over disease recurrence
- Concern over chronic GVHD
  - Transplant benefit is often attributed to GVL effects and GVHD considered a necessary evil.
Is chronic GVHD Good or Bad?
Relative Risk of Treatment Failure (death or relapse) after allo transplant for good risk leukemia as a function of GVHD

Ocular sicca

Oral ulcers

Nail dystrophy

Skin sclerosis

Deep sclerosis

Infections

Disability

Quality of life

Endocrine

Metabolism

Nutrition

Pain

Bronchiolitis obliterans

Loss of bile ducts

Fasciitis

Skin ulcers

Spectrum of manifestations in chronic GVHD
Gvhd

Delay in referral
Increase in relapse
Increase in TRM

Delay Referral
Decline in PS
Chemo refractory
Is chronic GVHD Good or Bad?
Relative Risk of Treatment Failure (death or relapse) after allo transplant for good risk leukemia as a function of GVHD

89 patients syngeneic transplant. 30 intermediate grade lymphoma

Bierman et al, J Clin Oncol 21, 3744, 2003
Graft-Versus-Tumor Effects After Allogeneic Hematopoietic Cell Transplantation With Nonmyeloablative Conditioning

Frédéric Baron, Michael B. Maris, Brenda M. Sandmaier, Barry E. Storer, Mohamed Sorror, Razvan Diaconescu, Ann E. Woolfrey, Thomas R. Chauncey, Mary E.D. Flowers, Marco Mielcarek, David G. Maloney, and Rainer Storb

Patients and Methods
We analyzed GVT effects in 322 patients given grafts from HLA-matched related (n = 192) or unrelated donors (n = 130).

Results
Of the 221 patients with measurable disease at HCT, 126 (57%) achieved complete (n = 98) or partial (n = 28) remissions. In multivariate analysis, there was a higher probability trend of achieving complete remissions in patients with chronic extensive graft-versus-host disease (GVHD; \( P = .07 \)). One hundred eight patients (34%) relapsed or progressed. In multivariate analysis, achievement of full donor chimerism was associated with a decreased risk of relapse or progression \( (P = .002) \). Grade 2 to 4 acute GVHD had no significant impact on the risk of relapse or progression but was associated with increased risk of nonrelapse mortality and decreased probability of progression-free survival (PFS). Conversely, extensive chronic GVHD was associated with decreased risk of relapse or progression \( (P = .006) \) and increased probability of PFS \( (P = .003) \).

Graft-Versus-Host Disease and Graft-Versus-Tumor Effects After Allogeneic Hematopoietic Cell Transplantation

Patients and Methods
Patients received low-dose total-body irradiation ± fludarabine before HCT from HLA-matched related (n = 611) or unrelated (n = 481) donors, followed by mycophenolate mofetil and a calcineurin inhibitor to aid engraftment and control GVHD. Median patient age was 56 years (range, 7 to 75 years). Forty-five percent of patients had comorbidity scores of \( \geq 3 \). Median follow-up time was 5 years (range, 0.6 to 12.7 years).

Results
Depending on disease risk, comorbidities, and GVHD, lasting remissions were seen in 45% to 75% of patients, and 5-year survival ranged from 25% to 60%. At 5 years, the nonrelapse mortality (NRM) rate was 24%, and the relapse mortality rate was 34.5%. Most NRM was a result of GVHD. The most significant factors associated with GVHD-associated NRM were serious comorbidities and grafts from unrelated donors. Most relapses occurred early while the immune system was compromised. GVT effects were comparable after unrelated and related grafts. Chronic GVHD, but not acute GVHD, further increased GVT effects. The potential benefit associated with chronic GVHD was outweighed by increased NRM.
All-cause mortality in 1479 2+y survivors after allo HCT

Age Matched Controls
Transplant Survivors

<table>
<thead>
<tr>
<th></th>
<th>No GVHD 10y</th>
<th>GVHD 10y</th>
<th>RR NRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>92%</td>
<td>73%</td>
<td>3.4</td>
</tr>
</tbody>
</table>

All-cause mortality in 1479 2+y survivors after allo HCT

![Graph showing survival function estimate over years since HCT]

<table>
<thead>
<tr>
<th></th>
<th>No GVHD 10y</th>
<th>GVHD 10y</th>
<th>RR NRM</th>
<th>RR RRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>92%</td>
<td>73%</td>
<td>3.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*Age Matched Controls*

*Transplant Survivors*
Impact of chronic graft-versus-host disease on late relapse and survival on 7489 patients after myeloablative allogeneic hematopoietic cell transplantation for leukemia

Conclusions: These results indicate that clinically relevant anti-leukemia effects of cGVHD on late relapses are present only in CML but not in AML, ALL or MDS. Chronic GVHD in patients who are one year survivors after myeloablative allogeneic HCT is primarily associated with higher TRM and inferior survival.
GVL and non-myeloablative tx

- GVL can induce/maintain remission in isolated cases
- IBMTR data on 2nd tx indicate that conditioning matters
- Syngeneic data suggest that GVL plays, on average, only a minor role in disease control
- Alternative approach:
  - Maintain intensity
  - Avoid GVHD, avoid TRM
BEAM Campath and aggressive NHL

Truelove et al, BBMT 21, 483, 2015
8/8 Allele, Available-Match Rates in the Adult Donor Registry
Donor Chimerism
Cord Blood Graft
Haplo-identical Graft
CD34-Selected

Magro et al, Haematologica 91, 540, 2006,
Liu et al, Blood 118, 6438, 2011
NEUTROPHIL AND PLATELET ENGRAFTMENT

Presented by: Koen van Besien, MD, PhD
INCIDENCE OF ACUTE AND CHRONIC GVHD
## Haplo Cord for Lymphoma

<table>
<thead>
<tr>
<th>Age</th>
<th>54 (24-72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>HL</td>
<td>5</td>
</tr>
<tr>
<td>CLL</td>
<td>5 (1 Richter)</td>
</tr>
<tr>
<td>MCL</td>
<td>3 (2 Blastoid)</td>
</tr>
<tr>
<td>DLBCL (MYC)</td>
<td>2</td>
</tr>
<tr>
<td>FL Transformed</td>
<td>1</td>
</tr>
<tr>
<td>MF</td>
<td>2</td>
</tr>
<tr>
<td>PTCL</td>
<td>4 (ALCL, AngImm, HS)</td>
</tr>
<tr>
<td>Chemo Response</td>
<td></td>
</tr>
<tr>
<td>Refractory (less than PR)</td>
<td>11</td>
</tr>
<tr>
<td>Chemo Sensitive</td>
<td>11</td>
</tr>
</tbody>
</table>

MFU Survivors: 11 months (2-71)
Survival after HC for lymphoma

Survival after Haplo Cord of Patients with Lymphoid Malignancies (n=22)
Case 1: 36 y SC panniculitis like gamma delta T cell lymphoma

- 7/2012: SQ, breast, liver, LN, spleen LDH 784 (nl250), hemophagocytosis
- EPOCH transient response, kinetic failure, ongoing hemophagocytosis.
- 11/2012: Flu-Mel-ATG +DUCBT
- Post tx: EBV neg B cell PTLD treated with rituximab.
- 10/2014: Ongoing remission. No GVHD
Pt 2: 64 y O Transformed lymphoma

- 11/09 stage 3 (BM negative) follicular grade II lymphoma (predominantly diffuse with sclerosis). watchful waiting)
- 11/11-4/12: Benda rituxan x6 with CR
- May 2013 relapse with LN, spleen pleural pericardial effusion. increased LDH.
- Referred for auto BMT but fails collection.
- PET PD. → RICE x1 with PR
- Comorbidities: Afib, DM
- 1/2014: HC SCT Flu Mel ATG
- 1/2015: Ongoing remission, no GVHD
Pt 3: 67 DLBCL Lymphoma

- 1995 DLBCL: CHOP + Bexxar (study)
- 2005: relapse: Intermittent rituxan
- 2013: bone marrow, PB, LDH 3000, t(8;14) MYC rearrangement, + additional cytogenetic abnormalities
- VIPERx 4→ residual marrow necrosis, LDH nl
- Comorbidities CHF, DM, PS: 60
- 12/2013: HC
- Multiple marrows with ongoing necrosis
- 03/2015: remission, limited cGVHD (vitiligo)
Allogeneic Transplantation

- Excellent treatment for pts unlikely to respond to autologous, failed autologous, failure to collect stem cells.
- GVHD is associated with worse survival, worse QOL and there is no evidence that it reduces relapse rates in lymphoma.
- Age is not a contra-indication.
- Suitable donors can be identified for nearly all patients.
- LDH rather than PET may be predictor
LETTER TO THE EDITOR

Programmed haploidentical hematopoietic stem cell infusion combined with systemic chemotherapy improves the outcomes of patients with refractory or relapsed lymphoma

Zhao Hong-Xia¹, Sun Wan-Jun¹, Li Jie¹, Hu Hai-Lan¹ & Ai Hui-Sheng²
<table>
<thead>
<tr>
<th>Prior Rx</th>
<th>Duration of Previous R</th>
<th>Best Prior R</th>
<th>Cell Dose CD34/CD3</th>
<th>Cell Dose CD34/CD3</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCL</td>
<td>RCHOP</td>
<td>PD</td>
<td>2.44/0.56</td>
<td>D 16 m PD</td>
</tr>
<tr>
<td>BL</td>
<td>CHOP</td>
<td>CR</td>
<td>1.51/0.9</td>
<td>DFS 41 m</td>
</tr>
<tr>
<td>T-LBL</td>
<td>VMCP</td>
<td>CR</td>
<td>2.1/0.7</td>
<td>DFS 41 m</td>
</tr>
<tr>
<td>T-LBL</td>
<td>VMCP</td>
<td>CR</td>
<td>2.7/0.9</td>
<td>DFS 31 mo</td>
</tr>
<tr>
<td>T-LBL</td>
<td>EPOCH</td>
<td>CR</td>
<td>2.8/1.8</td>
<td>DFS 28 mo</td>
</tr>
<tr>
<td>DLBCL</td>
<td>RCHOP</td>
<td>PD</td>
<td>0.7/.9</td>
<td>D 4 m PD</td>
</tr>
<tr>
<td>DLBCL</td>
<td>RCHOP</td>
<td>PD</td>
<td>0.9/0.2</td>
<td>D 10 m PD</td>
</tr>
<tr>
<td>MCHL</td>
<td>ABVD</td>
<td>PD</td>
<td>0.8/0.7</td>
<td>DFS 31 mo</td>
</tr>
<tr>
<td>MCHL</td>
<td>MOPP ABVD BEACOPP</td>
<td>CR</td>
<td>2.6/0.6</td>
<td>D 3 m inf</td>
</tr>
<tr>
<td>MCHL</td>
<td>ABVD BEACOPP</td>
<td>CR</td>
<td>2.9/07</td>
<td>DFS 19 m</td>
</tr>
</tbody>
</table>