Allogeneic Stem Cell Transplantation In Follicular Lymphoma

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Introduction

• Beneficial aspects of alloSCT in FL
• How to do an alloSCT in FL
• When to do an alloSCT in FL
Follicular Lymphoma

• Indolent, chronic disease BUT with variable clinical course
  – Median survival 10-16 years
  – High grade transformation in 30%
• Rapidly evolving treatment strategies
  – R-chemo-R
  – Second line therapies
  – Novel therapies
• AlloSCT for FL
  – Effective
  – Associated with significant toxicity
• What is the role of alloSCT?
EBMT Registry: SCT for FL 1990-2009

FL: Type of SCT By Year

Number of SCT

AutoSCT  AlloSCT
What are the benefits of an allogeneic SCT in FL?

• Durable disease control even in advanced disease
• Lower relapse rates compared to autologous SCT
  – The Graft versus follicular lymphoma effect?
  – Provision of a perfectly purged marrow?
• No late MDS/AML
Relapse Following HDT IN LGNHL (CIBMTR van Besien 2003)
Relapse Rate Following AutoSCT or Reduced Intensity AlloSCT For Relapsed FL?

\[ p < 0.001 \]

AUTO (n=726)

RIC (n=149)

Months after SCT

(Robinson BMT 2013)
RIC salvage for autoSCT failure

**FL** (Heidelberg, n=10)

**CLL** (GCLLSG, n=23)

(Courtesy of Peter Dreger)
Reduced Intensity AlloSCT For FL Relapsing after AutoSCT

At two years, DFS = 56.7 %

(EBMT Unpublished Data)
What is the benefit of an allogeneic SCT in FL?

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Efficacy Of Donor Lymphocyte Infusions In Follicular Lymphoma—Evidence For The GVL Effect

<table>
<thead>
<tr>
<th>Study</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris Blood 2004</td>
<td>4/6</td>
</tr>
<tr>
<td>Ingram BJH 2008</td>
<td>4/6</td>
</tr>
<tr>
<td>Corradini Leukaemia 2007</td>
<td>2/4</td>
</tr>
<tr>
<td>Thompson JCO 2010</td>
<td>10/13</td>
</tr>
</tbody>
</table>
Relapse Rate After Syngeneic, Autologous and Allogeneic SCT in LGNHL (Bierman 2003)

“Purging Effect”
Syngeneic AutoSCT
RR 11% 35-60%

“GVL Effect”
Syngeneic AlloSCT
RR 11% 15%
What is the benefit of an allogeneic SCT in FL?

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• No late MDS/AML
Secondary Malignancies After Upfront AutoSCT In FL

(Gyan Blood 2009;113:995)

A

All secondary malignances

B

sMDS/AML

Second cancers

$P = .014$

Time (months)

Cumulative incidence

0.0
0.2
0.4
0.6
0.8
1.0

0 20 40 60 80 100 120 140

Cumulative incidence

HDT Arm
What is the benefit of an allogenic SCT in FL?

• Durable disease control even in advanced disease
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• BUT AlloSCT STILL ASSOCIATED WITH SIGNIFICANT TOXICITY
How To Do An AlloSCT In Follicular Lymphoma

• Reduced intensity or myeloablative conditioning?
• T Cell Depletion?
• Donor Source
  – Sibling?
  – Volunteer Unrelated Donor?
  – Cord?
  – Haplo?
Reduced Intensity vs Myeloablative Conditioning in FL? CIBMTR

Relapse CI, n=208

NRM, n=208

(Hari et al, BBMT 2008)
Reduced Intensity vs Myeloablative Conditioning in FL? CIBMTR

(Hari et al, BBMT 2008)
Adverse Factors For PFS In AlloSCT For FL

<table>
<thead>
<tr>
<th>Variable</th>
<th>CIBMTR</th>
<th>EBMT</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>208 sib</td>
<td>131 MUD</td>
</tr>
<tr>
<td>Age</td>
<td>n.i.</td>
<td>++</td>
</tr>
<tr>
<td>Poor PS</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Refr. at SCT</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>MAC (vs RIC)</td>
<td>-</td>
<td>++</td>
</tr>
</tbody>
</table>

(Hari BBMT 2008; Avivi BJH 2009)
Outcome of BEAM-autologous and BEAM-alemtuzumab allogeneic transplantation in relapsed advanced stage follicular lymphoma
Which Regimen Intensity For AlloSCT In FL?

• No prospective studies comparing conditioning regimen intensity
• Reduced intensity conditioning most commonly employed in FL
• Reduced intensity conditioning appropriate for age distribution of FL patients
• FM+/-C
• FCR
• Intermediate intensity regimens BEAM/LACE?
How To Do An AlloSCT In Follicular Lymphoma

• Reduced intensity or myeloablative conditioning?

• T Cell Depletion?

• Donor source
  – Sibling?
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  – Cord?
  – Haplo?
T Cell Depleted RIC AlloSCT

N 82
Age 45 (26-65)
Median F/U 43 mo (5-117)
Diag-Tpt 46 mo
Prior Rx 4 (1-8)
Prior Auto 21 (26%)
Sib 39
MUD 33
MMUD 10

(Thomson K et al. JCO 2010 28, 3695-3700)
T Cell Depleted RIC AlloSCT
(Thomson et al 2010)

• Low incidence of GVHD
  – 13% acute GVHD grades I-III
  – 18% extensive chronic GVHD

• Impact of DLI
  – 10/13 responded
RICAlloSCT In FL.
The MD Anderson Experience

N 47
Age 53 (33-68)
Median F/U 60 mo (19-94)
Diag-Tpt 3yr (0.7-24)
Prior Auto 9 (19%)
Sib 45
MUD 2
Conditioning FCR

OS=85%
PFS=83%

(Khouri I et al. Blood 2008, 111, 5530-5536)
T Cell Depletion For AlloSCT In FL

- Both T replete and deplete protocols effective
- No prospective comparative data
- TCD abrogates GVHD
  - Must use DLIs preemptively
- More opportunistic infections with TCD
- Indolent nature of FL may permit use of TCD+preemptive DLIs
How To Do An AlloSCT In Follicular Lymphoma

• Reduced intensity or myeloablative conditioning?
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(Thomson K et al. JCO 28, 3695-3700)
MUD AlloSCT For Follicular Lymphoma

(Avivi BJH 2009)
How to do an alloSCT in FL

• Reduced-intermediate intensity conditioning
  – FMC, BEAM-C, LACE-C
  – FCR

• TCD abrogates GVHD
  – If TCD then use DLIs

• Consider sibling, matched unrelated donor (8/8 or 10/10) and cord blood options.

• Further studies of haploidentical SCT required in FL
When to do an alloSCT in FL?
### Stem Cell Transplantation In Follicular Lymphoma

**BSBMT Indications: Current Proposals**

<table>
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<tr>
<th></th>
<th>Autograft</th>
<th>Sibling transplant</th>
<th>MUD transplant</th>
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<tr>
<td>CR1/PR1</td>
<td>GNR&lt;sup&gt;1&lt;/sup&gt;</td>
<td>GNR</td>
<td>GNR</td>
</tr>
<tr>
<td>CR/PR&gt;1</td>
<td>S&lt;sup&gt;2&lt;/sup&gt;</td>
<td>CO&lt;sup&gt;3&lt;/sup&gt;</td>
<td>CO&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chemorefractory</td>
<td>GNR</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Relapse post autograft</td>
<td>GNR</td>
<td>S&lt;sup&gt;4&lt;/sup&gt;</td>
<td>S&lt;sup&gt;4&lt;/sup&gt;</td>
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**Abbreviations**

- **S** = Standard Indication
- **CO** = Clinical Option
- **GNR** = Generally Not Recommended
- **D** = Developmental
Only prospective comparative study of autoSCT vs chemotherapy for relapsed FL
Survival advantage for autoSCT
Pre Rituximab era
Small numbers

(Schouten HC  J Clin Oncol 2003; 21:3918-3927)
Is AutoSCT Curative In FL?
Long-term follow-up of autoSCT in FL

2nd-line autoSCT (Remission duration, n=121)

1st or 2nd-line autoSCT (PFS, n=241)

(Rohatiner et al, JCO 2007) (Kornacker et al, Ann Oncol 2009)
Outcome of ASCT In FL

1979-1995, median follow up 10 years
N=693

(Montoto Leukeamia 2008)
Autologous or Allogeneic Stem Cell Transplantation In FL?
AutoSCT vs RIC AlloSCT in Relapsed FL: an EBMT Study

- No prospective studies completed
- Retrospective comparison
- Patients with FL beyond 1\textsuperscript{st} response undergoing a 1\textsuperscript{st} SCT procedure
- 726 AutoSCT patients
- 149 RICalloSCT patients

(Robinson BMT 2013)
AutoSCT or RICalloSCT For Relapsed FL?

First SCT
Auto 726
RICalloSCT 149

(Robinson BMT 2013)
AutoSCT or RICalloSCT For Relapsed FL?

(Robinson BMT 2013)
AutoSCT or RICalloSCT For Relapsed FL?

(Robinson BMT 2013)
AutoSCT vs RICAlloSCT in FL?

- RICAlloSCT higher NRM
- RICAlloSCT lower relapse rate
- Overall Survival advantage not clear
- PFS survival advantage with RIC AlloSCT? (younger patients with sibling donors)
- Prospective studies required
## Stem Cell Transplantation In Follicular Lymphoma

### BSBMT Indications: Current Proposals

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<td>S(^2)</td>
<td>CO(^3)</td>
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<td>S(^4)</td>
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\(^{1,2,3,4}\) Standard Indication, Clinical Option, Generally Not Recommended, Developmental.
RICalloSCT For FL Relapsing after AutoSCT

• Paucity of data
• No published studies looking specifically at this setting
  – Branson 2002 RICalloSCT post autoSCT In LPD 1 case of LGNHL
• Most published studies of RICalloSCT in FL include a variable number of autograft failures
  – Thomson 2010 21 of 82
  – Rezvani 2008 20 of 62
  – Khouri 2008 9 of 47
  – Vigouroux 2007 25 of 73
RIC salvage for autoSCT failure

**FL** (Heidelberg, n=10)  
**CLL** (GCLLSG, n=23)

(Courtesy Of Peter Dreger)
RICalloSCT For FL Relapsing after AutoSCT

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<th>N</th>
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<tr>
<td>Median Age</td>
<td>44</td>
</tr>
<tr>
<td>Diag-AlloSCT</td>
<td>62 months</td>
</tr>
<tr>
<td>Auto-AlloSCT</td>
<td>23 months</td>
</tr>
<tr>
<td>Sibling</td>
<td>43%</td>
</tr>
<tr>
<td>UD</td>
<td>57%</td>
</tr>
<tr>
<td>Chemosensitive</td>
<td>77%</td>
</tr>
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</table>

At two years,
IR = 20.1 %
NRM = 23.1 %

(EBMT Unpublished Data)
RICalloSCT For FL Relapsing after AutoSCT

At two years, OS = 62.2%

Median FU of surviving patients = 33.5 months

(EBMT Unpublished Data)
RICalloSCT For FL Relapsing after AutoSCT

At two years, DFS = 56.7%
Reduced Intensity AlloSCT In FL

• Effective disease control even in advanced disease, PFS 60-80%
• TCD abrogates GVHD
• DLI effective for relapse post RIC alloSCT
• Which conditioning regimen?
  – FMC
  – FCR
  – BEAM
  – LACE
Which SCT Strategy In Relapsed FL?

• AutoSCT as first SCT?
• RICalloSCT as first SCT?
• AutoSCT followed by RICalloSCT?

• What about non-transplant therapies?
How should transplantation be integrated into the management of relapsed FL?
Integrating SCT Into Management Of FL?

SCT Therapy?

1st Line  2nd Line  3rd Line  nth Line

Clinical Course Of Follicular Lymphoma
Decision Making In FL

Patient Profile
- Age
- Performance status
- Co-morbidities
- Transplant specific comorbidity index
- Patient wishes

Disease Profile
- Time from diagnosis
- Duration of last response
- Quality of last response
- FLIPI at diagnosis and relapse
- Transformation

Treatment Profile
- Prior therapy
- Non-transplant therapies?
- Autologous stem cells?
- Sibling donor?
- MUD/Cord available?

Transplant Candidate?

Prognosis?

Available Therapies?
Acknowledgements

- EBMT Centers
- EBMT LWP
  - Ariane Boumendil
  - Herve Finel
  - Silvia Montoto
  - Peter Dreger
- BSBMT
Survival after relapse after autologous stem-cell transplantation (n = 103): all patients (A); by time interval from autoSCT to relapse (B; black line, >12 months; grey line, ≤12 months); by time of autoSCT (C; black line, upfront; grey line, salvage); patients with salvage autoSCT only by time interval from autoSCT to relapse (D; black line, >12 months; grey line, ≤12 months).