Transplantation for DLBCL & Follicular Lymphoma

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January 17, 2017
Disclosures

Research support:
- Takeda, Otsuka, Spectrum, Sanofi

Speakers Bureau:
- Otsuka Pharmaceuticals; Celgene, Inc. (Inactive)
- Sanofi

Consultancy:
- Cellerant Therapeutics
- MedImmune
- Celgene, Inc.
- Janssen R & D
Presentation Outline

• HCT utilization trends in hematological malignancies

• Current state of HCT in:
  – Diffuse Large B-cell Lymphoma
  – Follicular Lymphoma
Annual Number of Transplant Recipients in the US by Transplant Type (All Indications)

* 2014 Data incomplete
Non-Hodgkin and Hodgkin Lymphoma Patients Undergoing Matched Donor AlloHCT from 2000-2013

- Matched Sibling
- Matched Unrelated
Durable Control - An Unmet Need in Relapsed Lymphomas

• DLBCL: Relapsed or primary refractory disease
• Follicular: Early failure (≤2 years) or multiply relapsed disease
• Genomically high-risk disease
Presentation Outline

• HCT utilization trends in hematological malignancies

• Current state of HCT in:
  – Diffuse Large B-cell Lymphoma
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Autologous Transplantation for DLBCL Between 2006-2015

Number of Patients

Year of Transplant

In **relapsed** DLBCL, responding to salvage chemotherapy, autologous HCT remains standard-of-care.
AutoHCT after early R-CHOP failure?

CORAL Trial

Relapse ≤1 year after diagnosis

Relapse >1 year after diagnosis

Gisselbrecht C. JCO. 2010;28:4184-90
AutoHCT after early R-CHOP failure?

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Progression-free Survival

Early Failure (n=297)

Late Failure (n=214)

Overall Survival

Early Failure (n=297)

Late Failure (n=216)

Hamadani M. BBMT. 2014;20:1729-36.
DLBCL & HCT: Areas of Controversy

– Prevention of post auto-HCT relapse
– Upfront HCT for clinically high-risk DLBCL
– Upfront auto for genomic high-risk DLBCL
– Identifying ultra high-risk DLBCL
– Is there still a role for allogeneic HCT?
**AutoHCT after early R-CHOP failure?**

**CIBMTR DATA**

**Progression-free Survival**

**Overall Survival**

AutoHCT after early R-CHOP failure?

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AutoHCT after early R-CHOP failure?

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PFS-Landmark Analysis

OS-Landmark Analysis

Hamadani M. BBMT. 2014;20:1729-36.
BMT-CTN 1201: Post AutoHCT Ibrutinib Maintenance

Relapsed/Refractory DLBCL-ABC
Salvage ≥PR, stem cells collected

Randomization

Arm A

ASCT:
+ Ibrutinib 560 mg until day -1

Ibrutinib x 12 months

Follow Up

Arm B

ASCT:
+ Placebo

Placebo x 12 months

Follow Up
DLBCL & HCT: Areas of Controversy

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– Is there still a role for allogeneic HCT?
Upfront Autologous HCT for DLBCL

Stiff P. NEJM. 2013;369:1681-90.
Upfront Autologous HCT for DLBCL

Upfront Autologous HCT for DLBCL

- New DLBCL
- Inter-high or
- High IPI

Randomize

R-CHOP14 x8

ITT Results

DLBCL & HCT: Areas of Controversy

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Double-Hit DLBCL (DHL)

- DLBCL with rearrangement of c-MYC plus BCL2 and/or BCL6
  - 5-10% of newly diagnosed DLBCL
  - Dismal prognosis with standard R-CHOP


FISH with dual color break-apart probes for MYC, BCL2, BCL6. Photos courtesy of V. Bedell, 63x Bioview imaging system.
MYC/BCL2 Double Expressing DLBCL (DEL)

- DLBCL with coexpression of c-MYC and BCL2 proteins by immunohistochemistry
  - 21-34% of newly diagnosed DLBCL
  - Poor outcomes after R-CHOP, independent of other factors

Photos courtesy of S. Rodig, 1000x
Outcomes in DEL and DHL after R-CHOP

Johnson N. JCO. 2012;30:3452-9
DHL & Upfront Autologous HCT

EPOCH-like induction

R-CHOP induction

Relapse Free Survival

P < 0.001

Months

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Landsburg D. ASH abs. 2016
DLBCL & HCT: Areas of Controversy

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## REFINE Study – Ultra High-risk DLBCL

<table>
<thead>
<tr>
<th></th>
<th>HR (95% C.I.)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early relapse</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Residual disease</td>
<td>1.33 (0.58-3.04)</td>
<td>0.49</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>2.46 (1.23-4.88)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>NCCN-IPI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intermediate-low</td>
<td>1.41 (0.46-4.28)</td>
<td>0.54</td>
</tr>
<tr>
<td>Inter-high/ High</td>
<td>3.16 (1.02-9.82)</td>
<td>0.047</td>
</tr>
<tr>
<td><strong>MYC Rearrangement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>3.52 (1.60-7.72)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Auto-HCT in Relapsed DEL and DHL DLBCL

![Graph showing progression-free survival over time from transplantation.]

- Blue line: Not DEL or DHL
- Gray line: DEL not DHL
- Yellow line: DHL

Time From Transplantation (months)

Progression-Free Survival (%)

DLBCL & HCT: Areas of Controversy

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Allogeneic HCT for DLBCL

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Chemosensitive DLBCL

Chemorefractory DLBCL


Hamadani M. BBMT. 2013:746-53.
Allogeneic HCT for DLBCL

CIBMTR DATA

Prognostic Factors:
- KPS < 80 = 4 points
- Chemoresistant = 5 points
- auto to alloHCT < 1yr = 2 points

3-year OS:
- Low = 43%
- Intermediate = 39%
- High = 19%
- Very High = 11%
Allogeneic HCT in Relapsed DEL DLBCL

4-year OS
DEL 31%, (95CI 16-47%)
Non-DEL 49%, (95CI 32-63%)

p = 0.17

Allogeneic HCT in Relapsed DHL DLBCL

4-year OS

DHL 50%, (95CI 18-75%)
Non-DHL 38%, (95CI 26-50%)  \[ p = 0.5 \]

DHL, n = 10
Non-DHL, n = 68

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Presentation Outline

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• Current state of HCT in:
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HCT for Relapsed Follicular Lymphoma?

Decision?

Relapsed or Refractory Follicular Lymphoma

- Autologous Transplantation
- Allogeneic Transplantation
Auto-HCT for Relapsed FL – CUP Trial

Relapsed FL
Age < 66yrs (N=140)

Chemotherapy

CR or PR?

RANDOMIZATION

Chemotherapy (n=24)

Purged-Auto (n=32)

Unpurged-Auto (n=33)

Progression-free Survival

Overall Survival

Is Autologous HCT Curative for Relapsed FL?

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## Is Autologous HCT Curative for Relapsed FL?

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>OS</th>
<th>Second Cancers</th>
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</thead>
<tbody>
<tr>
<td>Rohatiner (2007)</td>
<td>121</td>
<td>54% (10 years)</td>
<td>- 12.4% sMDS/AML</td>
</tr>
<tr>
<td>Montoto (2007)</td>
<td>693</td>
<td>52% (10 years)</td>
<td>- 9% sCA</td>
</tr>
<tr>
<td>Sebban (2008)</td>
<td>GELF-86, GELF-94, 254</td>
<td>+R/-T = 70%, +R/+T = 93% (5 years)</td>
<td>- Not reported</td>
</tr>
</tbody>
</table>
CTN #0202: AutoHCT vs RIC AlloHCT for Relapsed Follicular NHL

- Biologic assignment with matched sib donor
- Randomized: autoHCT vs RIC alloHCT
- N = 250 (projected)
- N = 30 (2004-2006)
- Closed early due to poor accrual
  - 22 autoHCT
  - 8 alloHCT

Median F/u = 36 mos

Slide Courtesy: Ginna Laport, MD
Auto vs. Allo for FL: CIBMTR Data

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>5-yr PFS</th>
<th>5-yr OS</th>
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</thead>
<tbody>
<tr>
<td>AutoHCT</td>
<td>249</td>
<td>41%</td>
<td>74%</td>
</tr>
<tr>
<td>AlloHCT</td>
<td>267</td>
<td>58%</td>
<td>66%</td>
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Auto vs. Allo for FL: CIBMTR Data
Long-term survivors

<table>
<thead>
<tr>
<th>Landmark</th>
<th>N</th>
<th>5-yr PFS</th>
<th>5-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AutoHCT</td>
<td>138</td>
<td>68%</td>
<td>91%</td>
</tr>
<tr>
<td>AlloHCT</td>
<td>138</td>
<td>92%</td>
<td>94%</td>
</tr>
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Autologous HCT for Follicular Lymphoma Between 2006-2015
Allogeneic HCT for Follicular Lymphoma Between 2006-2015

Number of Patients

Year of Transplant

MRD

MUD

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Autologous HCT Underutilized in U.S.A

• No more than 1-1.5% of follicular lymphoma patients in USA undergo autologous HCT

• An auto vs. allo (or non HCT therapy) trial is unlikely to be performed now

• Re-defining FL patients likely to benefit from HCT is an unmet need
Number of Prior Regimens often used to judge suitability of AutoHCT in FL


N = 121; Median F/U = 13yrs

Vose et al, BBMT 2008;14:36.

N = 248; Median F/U = 6yrs
Does Number of Prior Therapy Paradigm Hold true in Rituximab Era?

Progression-free Survival

Overall Survival

CIBMTR LY13-03 unpublished data
Early failure of R-chemo identifies an Ultra high-risk subset of FL:

National LymphoCare Study

Overall Survival

<table>
<thead>
<tr>
<th>OS, %</th>
<th>Early POD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year</td>
<td>68</td>
<td>97</td>
</tr>
<tr>
<td>5-year</td>
<td>50</td>
<td>90</td>
</tr>
</tbody>
</table>

Casulo C. JCO. 2015;33:2516-22.
Should autologous HCT be considered in UHR FL?

CIBMTR. Unpublished data
HCT in UHR FL: Key Registry Studies

- NLCS & CIBMTR Collaboration: Auto-HCT vs. no-HCT study. Results will be available 2017 BMT Tandem meetings.

- CIBMTR analysis of auto-HCT vs. allo-HCT underway. Results will be available 2017 ASCO meetings.
Questions for 2017 & Beyond

• Define role of upfront autoHCT in DHL/DEL
• Is autoHCT an option for relapse UHR DLBCL?
• In relapsed DEL/DHL should allogeneic HCT be investigated?
• Auto vs. Allo for NLCS defined UHR FL
• Urgent need for transplant registries to capture molecular risk-data (e.g. DHL/DEL status) and develop tissue bank
Acknowledgements

CIBMTR & LYWC

Slides used with permission

Gina Laport
Philippe Armand
Alex Herrera
Luciano J. Costa
Carla Casulo
Thank you!
Overall Survival in Follicular Lymphoma Patients

CIBMTR Data

Overall Survival

<table>
<thead>
<tr>
<th>Haplo-HCT</th>
<th>MRD</th>
</tr>
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<tbody>
<tr>
<td>3-years</td>
<td>70%</td>
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years

Probability, %

Haploidentical

HLA Identical Sibling
Overall Survival in DLBCL Patients

<table>
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<th>HLA Idenetical Sibling</th>
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<tbody>
<tr>
<td>3-years Haplo-HCT</td>
<td>59%</td>
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<tr>
<td>MRD</td>
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CIBMTR Data
Allogeneic Transplant for DLBCL Between 2006-2015

Year of Transplant

Number of Patients

MRD  MUD


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