Autologous Stem Cell Transplantation: Current Perspectives in Myeloma and Lymphoma

April 7, 2016

Welcome and Introductions
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Disclosures

• Consulting/Grant Support
  – Celgene

• Speakers Bureau/Grant Support
  – Bristol-Myers Squibb
Incidence of Myeloma by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Percent of New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0.0%</td>
</tr>
<tr>
<td>20-34</td>
<td>0.6%</td>
</tr>
<tr>
<td>35-44</td>
<td>3.1%</td>
</tr>
<tr>
<td>45-54</td>
<td>11.3%</td>
</tr>
<tr>
<td>55-64</td>
<td>23.2%</td>
</tr>
<tr>
<td>65-74</td>
<td>28.2%</td>
</tr>
<tr>
<td>75-84</td>
<td>24.3%</td>
</tr>
<tr>
<td>&gt;84</td>
<td>9.3%</td>
</tr>
</tbody>
</table>

Myeloma Symptoms: CRAB

C – elevated calcium
R – renal failure
A – anemia
B – bone disease

Active disease requires at least 30% plasma cells in the bone marrow
Trends in Overall Survival of MM


Diagnosis period Median OS
1996–2006 45 months
1971–1996 30 months
(P<0.001)

Overall survival 1971–2006

Meta-Analysis of Autologous Transplant vs Conventional Chemotherapy – Overall Survival

High-dose Therapy with Single Autologous Transplantation versus Chemotherapy for Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-analysis of Randomized Controlled Trials.

Improving Response Rates with Combination Therapies

Is There a Role for Transplant in the Era of Novel Drugs?

RVD × 3
- Stem collection
- Transplant
- RVD×2
- Revlimid Maintenance

RVD × 3
- Stem collection
- RVD×5
- Revlimid Maintenance
- Transplant at relapse

RVD, Revlimid (lenalidomide), Velcade (bortezomib), dexamethasone

NCI Clinical Trial Identifier NCT01191060.
Transplant Delays Disease Recurrence

<table>
<thead>
<tr>
<th></th>
<th>RVd + ASCT (n = 350)</th>
<th>RVd, no ASCT (n = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr PFS, %</td>
<td>61</td>
<td>48</td>
</tr>
<tr>
<td>Stratified log-rank $P &lt; .0002$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-yr OS, %</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Stratified log-rank $P = .25$</td>
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<td></td>
</tr>
<tr>
<td>CR, %</td>
<td>58</td>
<td>46</td>
</tr>
<tr>
<td>$P &lt; .01$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPM, n (%)</td>
<td>23 (6.6)</td>
<td>18 (5.1)</td>
</tr>
</tbody>
</table>

CR, complete response; OS, overall survival; PFS, progression-free survival; SPM, second primary malignancy

Depth of Response Correlates with Improved Outcomes

Martinez-Lopez et al Blood. 2011;118(3):529-534
Role of Revlimid Maintenance Following Transplant

- Revlimid increased the benefit of transplant
- Revlimid improved the progression free survival


The Role of Minimal Residual Disease on Myeloma Outcomes

- Patients with evidence of minimal residual disease benefitted from maintenance therapy

Hiroyuki Takamatsu et al., ASH 1788. Prognostic Value of Sequencing-Based Minimal Residual Disease Detection in Patients with Multiple Myeloma Who Underwent Autologous Stem Cell Transplantation
Maintenance Revlimid Improves Minimal Residual Disease

![Graph showing MRD at pre-maintenance for arm B](image)

P-value: $p < 0.0001$

N at risk (events)

<table>
<thead>
<tr>
<th></th>
<th>MRD negative</th>
<th>MRD positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>61</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>16</td>
</tr>
<tr>
<td>12</td>
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<td>18</td>
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<td>24</td>
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<td>30</td>
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<td>36</td>
<td>55</td>
<td>21</td>
</tr>
<tr>
<td>42</td>
<td>54</td>
<td>22</td>
</tr>
<tr>
<td>48</td>
<td>53</td>
<td>23</td>
</tr>
</tbody>
</table>

The Autologous Transplant Process

1. Collection
   Stem cells are collected from the patient's bone marrow or blood.

2. Processing
   Blood or bone marrow is processed in the laboratory to purify and concentrate the stem cells.

3. Cryopreservation
   Blood or bone marrow is frozen to preserve it.

4. Chemotherapy
   High dose chemotherapy and/or radiation therapy is given to the patient.

5. Reinfusion
   Thawed stem cells are reinfused into the patient.
An Approach to High-Risk Disease
Marrow Infiltrating Lymphocytes (MILs)

- Cells obtained from the bone marrow of patients
- Shown to have a high degree of myeloma activity
- Are grown in the lab and then given back to the patients
MILs Logistics

1. MILs harvested
2. MILs Expansion
3. Stem Cell Transplant
4. Reinfusion of MILs

MILs Trial for High-Risk Myeloma J1343 (n=90)

- MILs BM Harvest
- Mel 200 Auto SCT (Randomization 2:1)
- Tadalafil days 2-11
- MILs d+3, +4
- Tadalafil days 2-11
- Lenalidomide 5mg ~day 60 until disease progression
Joseph C. Alvarnas, MD

Director of Value Based Analytics
Director of Clinical Quality Based Analytics
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City of Hope
Duarte, CA

Disclosures

• Consulting
  – Juno Therapeutics

• Other
  – National Comprehensive Cancer Networks
    (Panel Co-Chair & Speaker)
  – The American Journal of Managed Care
    (Journal Editor/Meeting Speaker)

• Speakers Bureau
  – Ultimate Medical Learning Company
A Rapidly Evolving Understanding of Lymphoma

**Thomas Hodgkin**
Hodgkin Lymphoma

**From Morphology to a Genomic Understanding of Lymphomas**
- Hodgkin lymphoma first described in 1832
- First system for classifying non-Hodgkin lymphoma proposed 1956
- The World Health Organization (WHO) classification system now differentiates nearly 80 different forms of lymphoma
- Lymphomas initially described based upon the appearance of cells on pathology slides
- Modern description and classification of lymphomas include genetic, molecular, genomic, proteomic and viral information

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**Incidence of Non-Hodgkin (NHL) and Hodgkin Lymphoma (HL)**

- **NHL estimated new cases 2015 – 71,850**
  - 4.3% of all new cancer cases
  - Estimated deaths in 2015 - 19,790
  - Patients surviving 5 years – 70%
- **HL estimated new cases 2015 – 9,050**
  - 0.5% of all new cancer cases
  - Estimated deaths in 2015 – 1,150
  - Patients survival 5 years – 85.9%

Factors That Increase Risk of, or Contribute to, Development of Lymphomas

- Advancing age
- Inherited genetic disorders
  - Wiskott-Aldrich syndrome, X-linked hypogammaglobulinemia, Chédiak-Higashi, ataxia-telangiectasia syndrome
- Viral infections
  - Epstein barre virus
  - Cytomegalovirus
  - HHV-8
  - HIV infection
  - Human T-cell leukemia virus
  - Hepatitis C
- Bacterial infections
  - *Helicobacter pylori*

Hodgkin Lymphoma
(Reed-Sternberg Cells)
Diffuse Large B-cell Lymphoma

Burkitt Lymphoma
Characteristic Genetic Changes Associated with Burkitt Lymphoma

Characterizing Aggressive Non-Hodgkin Lymphoma on a Genomic Level
Immense Diversity of Lymphoma Subtypes

- WHO classification scheme differentiates many subtypes of NHL and HL (>65)
- Lymphoma treatment and prognosis differs markedly based upon subtype
- B-cell lymphomas are more common than T-cell derived lymphomas
- Lymphomas of follicular subtypes are typically less aggressive at presentation and associated with a more protracted course
- Diffuse large B-cell Lymphoma (DLBCL) is most common subtype (up to 40% of lymphomas diagnosed in US)
- Unlike some solid tumors, patients with relapsed or persistent lymphomas may have an important second chance for cure through the use of an autologous bone marrow/blood stem cell transplant

Autologous Blood Stem Cell Transplantation

Stem Cells from Self to the Rescue

- Stem cells are collected from patient
- Patient receives chemotherapy or radiation
- Self-donated stem cells are re-infused into patient
Cumulative Plot of Transplant Recipients in the US by Transplant Type

Autologous Hematopoietic Cell Transplantation BMT CTN/AMC 0803/071

HSC mobilization:
Per Institutional Standard

Apheresis and HSPC collection

Cryopreservation

Conditioning with BEAM:
BCNU, AraC VP16, AraC VP16, AraC VP16, AraC VP16, Melphalan

aHCT

*2014 Data incomplete
Collection of Autologous Blood Stem Cells

Autologous Stem Cell Transplantation
Reconstitution of Hematopoiesis After Transplantation

Criteria for Autologous Stem Cell Transplantation

- Chemotherapy-sensitive relapsed and persistent aggressive NHL
- Relapsed and persistent HL
- Adequate organ function to tolerate intensity of transplant process
- Ability to mobilize and collect adequate numbers of autologous blood stem cells
**Trends in Autologous Transplants by Recipient Age**

*Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma*

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**Indications for Hematopoietic Stem Cell Transplants in the US, 2013**

*Allogeneic (Total N=8,197)  Autologous (Total N=11,258)*
Survival After Autologous Transplants for Hodgkin Lymphoma, 2003-2013

Survival After Autologous Transplants for Follicular Lymphoma, 2003-2013
Survival After Autologous Transplants for Diffuse Large B-cell Lymphoma (DLBCL), 2003-2013

![Graph showing survival rates for sensitive and resistant DLBCL patients.]

Survival After Transplants for Mantle Cell Lymphoma, 2003-2013

![Graph showing survival rates for autologous and allogeneic transplantation.]

CIBMTR
HIV Infecting CD4+ T-cells

Autologous HCT for ARL

<table>
<thead>
<tr>
<th>Publication</th>
<th>Failure to mobilize</th>
<th>Patients (n)</th>
<th>Tx related mortality</th>
<th>Median f/u (months)</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krishnan et al. 2005</td>
<td>0</td>
<td>20</td>
<td>5%</td>
<td>32</td>
<td>85%</td>
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<tr>
<td>Spitzer et al. 2008</td>
<td>2</td>
<td>20</td>
<td>5%</td>
<td>5.8</td>
<td>&gt;50%</td>
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<tr>
<td>Re et al. 2003</td>
<td>4</td>
<td>10</td>
<td>0</td>
<td>18</td>
<td>39%</td>
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<tr>
<td>Re et al. 2009</td>
<td>6</td>
<td>27</td>
<td>0</td>
<td>44</td>
<td>75%</td>
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<tr>
<td>Gabare et al. 2004</td>
<td>NA</td>
<td>14</td>
<td>NA</td>
<td>1</td>
<td>71%</td>
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<tr>
<td>Serrano et al. 2005</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>32</td>
<td>73%</td>
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<tr>
<td>Balsalobre 2009</td>
<td>NA</td>
<td>68</td>
<td>7.5%</td>
<td>32</td>
<td>61%</td>
</tr>
</tbody>
</table>

First case report: Gabare et al, BMT 1996; 18: 1195-7
Progression-free Survival

Overall Survival: HIV-Infected Patients vs. 151 CIBMTR non-HIV-infected Patients
Growing Armamentarium of Immunotherapeutic Agents for B-cell Malignancies

- Monoclonal antibodies
  - Rituximab in NHL
  - CAMPATH in CLL
- Monoclonal antibody-drug conjugates
  - Brentuximab
  - Inotuzumab
- Bi-specific antibodies
  - Blinatumomab
- T-cell based therapeutics*
  - Chimeric antigen receptor T-cells
Problem: Current Outcomes in Diffuse Large B-cell Lymphoma and Mantle Cell Lymphoma Are Not Acceptable!

- DLBCL is the most common subtype of NHL (30%). Survival without treatment is measured in months.
- Up to 70% of patients have advanced stage disease at diagnosis
- With standard treatment, 60% of patients are still alive and disease free at 5 years.
- Patients who relapse or who cannot achieve first remission are not curable without transplant

CAR T-cell Therapeutics

- Form of adoptive immunotherapy
- Autologous T-cells engineered to express T-cell receptor (TCR) with CD19 specificity
- Target cells killed by T-cell specific tumor killing
- Important toxicities
  - Tumor lysis syndrome
  - Cytokine release syndrome
  - Macrophage activation syndrome
  - Neurological toxicities
  - B-cell aplasia
- In vivo persistence of CAR T-cells
Adoptive T Cell Therapy for Cancer

- T Cell Donor (Autologous or Allogeneic)
- Adoptive T cell Transfer
- Patient Recipient
- Isolate Cytotoxic T Lymphocyte
- Engineer Cytotoxic T Cells to Express Tumor Specific Chimeric Antigen Receptors
- Expand Tumor Specific T Cells Ex Vivo

Platform for Manufacturing $T_{CM}$ Derived CD19CAR+ T Cells

Day 1: Leukapheresis
Day 2: CliMiMACS Selection of Tcm; Dynabead stimulation
Day 5: Lentiviral Transduction; Initiate Expansion
Day 14-30: Dynabead Removal
Day 26-40: Cryopreservation
Promise and Risks of CAR T-cell Therapeutics

- CAR T-cells and other T-cell therapeutics are under study in clinical trials
- Potential risks of CAR T-cells based treatments include
  - Cytokine release syndrome
  - Tumor lysis syndrome
  - Neurological toxicities
  - Persisting low B-cell counts

Summary and Future Directions

- Treatment for patients with relapsed and refractory NHL and HL is increasingly effective
- Autologous transplant is an important component in the cure of many patients with relapsed or persistent aggressive NHL and HL
- Patient with HIV infection have transplant outcomes equivalent to those of patients without HIV-infection
- T-cell-based therapeutics may allow us to improve upon the success of autologous transplant
Why This Work is Never Complete

Autologous Stem Cell Transplantation: Current Perspectives in Myeloma and Lymphoma

Question & Answer Session
The speaker’s slides are available for download at www.LLS.org/programs
The Leukemia & Lymphoma Society (LLS) offers:

- Live, weekly Online Chats are moderated by an oncology social worker and provide a friendly forum to share experiences.
  ➢ WEBSITE: www.LLS.org/chat

- What to ask: For a list of suggested questions to ask about certain topics, download and print any of the following guides.
  ➢ WEBSITE: www.LLS.org/whattoask

- Free publications are available ranging from disease specific information to health insurance options and resources to help patients and their families cope with the financial aspects of cancer.
  ➢ WEBSITE: www.LLS.org/booklets

- For more information about blood cancers and other LLS programs, please contact an LLS Information Specialist.
  ➢ TOLL-FREE PHONE: (800) 955-4572
  ➢ EMAIL: infocenter@LLS.org