Patient Selection for allogeneic stem cell transplantation – in CLL

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Topics

- CLL
- “Complicated CLL”
- Richter’s transformation
What did we learn about allo-transplant for CLL?

- Allogeneic Transplant can be Curative
- Myeloablative Conditioning has been virtually abandoned for patient over 50.
  - Rightly or Wrongly....
- TRM influenced by
  - KPS
  - Pre-existing immunosuppression
  - Comorbidity
  - Less so by age
  - Less by Donor type
- Cure Rates Depend on Achievement of CR
- GVL effects play a role in achievement and maintenance of CR
- Those in CR for more than a year have an excellent outcome.
Outcomes of HLA-identical donor vs Haplo-Cord Transplantation in patients with AML-MDS ≥ 50

Rhodes et al, ASH 2014
## Non-Myeloablative Transplant in 86 patients with CLL

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58 (36-70)</td>
</tr>
<tr>
<td>MRD/MUD</td>
<td>43/43</td>
</tr>
<tr>
<td>Time from Dx (mo)</td>
<td>62 (6-307)</td>
</tr>
<tr>
<td>Richter’s</td>
<td>19 (22%)</td>
</tr>
<tr>
<td>Binet stage B/C</td>
<td>85%</td>
</tr>
<tr>
<td>CD5 in marrow</td>
<td>29% (0-94)</td>
</tr>
<tr>
<td>PET/Ga Pos</td>
<td>33%</td>
</tr>
<tr>
<td>High LDH</td>
<td>42%</td>
</tr>
<tr>
<td>B symptoms</td>
<td>28%</td>
</tr>
<tr>
<td>Zap 70+</td>
<td>80%</td>
</tr>
<tr>
<td>Unmutated IgH</td>
<td>72%</td>
</tr>
<tr>
<td>P53+/p21-</td>
<td>23%</td>
</tr>
<tr>
<td>IgG low and CD4 low</td>
<td>22%</td>
</tr>
<tr>
<td>Fludara resistant</td>
<td>83%*</td>
</tr>
</tbody>
</table>

*But mostly low bulk disease*
Non-Myeloablative Transplant in 86 patients with CLL

- Non-Relapse Mortality
  - Day 100: 3%
  - One year: 17%

- Acute GVHD:
  - Grade II-IV: 37%
  - Grade III-IV: 7%
  - Chronic GVHD: 56% (7 after DLI)

- Age doesn’t matter
- Low CD4/IgG is adverse prognostic factor
- p53 does not matter

Khouri et al, Cancer 2011
There is no effect of 17 p

Schetelig et al, JCO 2008

Poon et al, Leukemia Lymphoma 2015
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GVL effects play a role in the achievement of CR

Khouri et al, Cancer 2011
Boetcher et al, Blood reviews 2011
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- Cure Rates Depend on Achievement of CR
- GVL effects play a role in achievement and maintenance of CR
- **Those in CR for more than a year have an excellent outcome.**
Remissions persisting beyond one year after allo SCT for CLL are durable

Impact of MRD status at 12 mo on Long term relapse rates

Durability of MRD negativity

Boeticher, 2011
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- Cure Rates Depend on Achievement of CR
- GVL effects play a role in achievement and maintenance of CR
- **Those in CR for more than a year have an excellent outcome.**
- **Prolonged Survival is possible after relapse**
Survival Richter's vs CLL

<table>
<thead>
<tr>
<th>Rx given -CLL</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab/Ofatumumab</td>
<td>43/28</td>
</tr>
<tr>
<td><em>Imid</em></td>
<td>25</td>
</tr>
<tr>
<td>Purine analog/BR</td>
<td>20/15</td>
</tr>
<tr>
<td>HCVAD-OFAR</td>
<td>28</td>
</tr>
<tr>
<td>BTK</td>
<td>5</td>
</tr>
<tr>
<td>DLI/2nd SCT</td>
<td>16/2</td>
</tr>
<tr>
<td>No Rx</td>
<td>4</td>
</tr>
</tbody>
</table>

Survival Richter's vs CLL

Survival aGVHD vs not

Survival cGVHD vs not

Rozovski et al JCO 2015
New Therapies have changed the paradigm….

- BTK inhibitors
- PI3Kinase inhibitors
- BCL2 inhibitors
Among those patients whose initial response was PR-L, the majority achieved classic response by IWCLL criteria:

- TN: 9/13 (69%)
- R/R: 38/49 (78%)

Combined ORR + (PR-L):
- TN = (84%)
- R/R = (88%)
Ibrutinib: Progression Free Survival

Furman RR. IWCLL 2013.

No del17p or del11q est. PFS = 92.2%

del11q est. PFS = 72.9%

del17p est. PFS = 53.1%

TN est. PFS = 96.3%

R/R est. PFS = 73.6%

At 26 months:
For Now…

- Patients failing BTK inhibitors
- Patients with 17p abnormalities.
For now

- CLL: multiply relapsed – 17p
- “Complicated CLL”
- Richter’s transformation
Patient 1

- Male, 38
- PMH:
- PSH:
- Never smoked

Patient 2

- Male 57
- PMH: Bipolar, DM, cardiomyopathy, melanoma, fungal infection, cellulitis partial small bowel removal, GERD, obesity
- Never smoker
Patient 1
The Disease

- **CLL dx in 2008 (age 34)**
  - **Treatment:**
    - FIR → CR x 1 y
    - FR x6 → PD
    - CAT8015 (anti CD22) → Cap Leak
    - Ofatumumab → PD
    - Benda Rituximab → PD
    - HD MP +Rituximab → PD
  - **Current status:**
    - Profoundly pancytopenic.
    - Tx dependent
    - Possible MDS
    - Iron overload

Patient 2
The Disease

- **CLL dx in 2002 (age 47)**
  - **Treatment:**
    - CVP x6
    - FR x5
    - PCR x23
    - Benda-R
    - Cytoxan-doxorubicin-VP-PDN
    - MTX-VCR
    - Chlorambucil
    - Thalidomide
    - Alemtuzumab
    - HDMP +Ofatumumab IVIG
    - Alemtuzumab
    - 2010: PCI-32765
  - **Current status:**
    - Profoundly pancytopenic.
    - Tx dependent
    - Cytogenetics 46, XY(del20), (q11.2)
Patient 1
Outcomes

- No related or unrelated donor
- Haplo Cord Transplant
  - Conditioning Fludarabine MeI ATG
- Engrafted d15
- Post Tx complications:
  - Adenovirus viremia/pharyngitis
  - Transient poly arthritis –(Dciff?)
  - Hives
- Currently 26 mo post tx
  - CLL MRD neg
  - No GVHD
  - Perfect health
  - Phlebotomies for Iron overload

Magro et al, Haematologica 91, 540, 2006,
Liu et al, Blood 118, 6438, 2011
Patient 1

Outcome

- No related or unrelated donor
- Haplo Cord Transplant
  - Conditioning Fludarabine Mel ATG
- Engrafted d15
- Post Tx complications:
  - Adenovirus viremia
  - Transient poly arthritis
- Currently 28 mo post tx
  - No GVHD
  - Perfect health
  - MRD negative
  - Phlebotomies for Iron overload

Patient 2

Outcome

- Unrelated donor
- MUD transplant
  - Conditioning Fludarabine Melphalan Alemtuzumab
- Engrafted d15
- Post Tx complications
  - Strep mitis sepsis
  - Acute GVHD gr II
- Currently 38 months post tx
  - No GVHD
  - Good health
  - MRD 0.2%
For now

- CLL multiply relapsed, 17p
- “Complicated CLL”
- Richter’s transformation
Survival in patients who responded to initial therapy by subsequent stem-cell transplantation (SCT).

Apostolia-Maria Tsimberidou et al. JCO 2006;24:2343-2351
Patient 3

- 71 year old male
- Hx of smoking, mild emphysema
- 10 yr hx of stage 0-1 CLL: no treatment
- New Gallium Avid lymphadenopathy
- Bx: DLBCL ---Ig sequencing clonally related.
- RCHOP: CR with residual uptake in lung lesion
Conclusion

- Allo SCT continues to be the only curative therapy.
- Indications are rapidly changing and include
  - Failure of first line therapy -17 P
  - T-MDS/AML
  - Richter’s
- Outcomes are dependent on
  - Disease response
  - Degree of immunosuppression
  - NOT
    - Donor Type
    - Age
- Challenge: Avoidance of Chronic GVHD and maximizing GVL
  - Allo Transplant + post-transplant maintenance?
Thanks

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Pharmacy
Apheresis
Stem Cell Lab

PATIENTS AND STEM CELL DONORS