Should all adult ALL patients have a stem cell transplantation in first remission

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COHEM
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Adult ALL

- Has a poor outcome with only a minority of patients cured
- Most patients achieve CR but few remain in remission & a significant proportion die in CR (with transplant or chemotherapy)
- Careful risk: benefit analysis is the only way to assign current therapies appropriately – intensifying the treatment for some but reducing intensity for others
Risk

Can be defined *before* treatment and/or redefined *during* it

- MRD, which can possibly better define allo and auto transplant candidates
Who is an “adult”?

AND

What defines “standard” and “high risk”? 
### Standard & high risk disease defined at diagnosis

**Ph**\(^\text{neg} \) ALL – MRC UKALL XII / ECOG 2993

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Standard Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any of the following:</td>
<td>None of the following:</td>
</tr>
<tr>
<td><strong>Age</strong> ( \geq 35 ) years</td>
<td></td>
</tr>
<tr>
<td>WBC ( &gt; 30,000/\mu\text{L} ) (( B ) Lineage)</td>
<td></td>
</tr>
<tr>
<td>( &gt; 100,000/\mu\text{L} ) (( T ) Lineage)</td>
<td></td>
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<tr>
<td>Time to CR ( &gt; 4 ) weeks</td>
<td></td>
</tr>
<tr>
<td>( t(4;11), t(8;14), ) complex karyotype, low hypodiploidy, triploidy</td>
<td></td>
</tr>
</tbody>
</table>

*BUT* others have slightly different definitions of pre treatment risk groups
MRC UKALL XII/ECOG 2993: overall survival from diagnosis
Ph\textsuperscript{neg} patients only

All patients

Standard risk

High risk

Goldstone et al 2008
# MUDs in Adult ALL

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>CR 1</th>
<th>OS %</th>
<th>DFS %</th>
<th>Relapse %</th>
<th>TRM %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kiehl et al 2004</strong></td>
<td>221</td>
<td></td>
<td></td>
<td>45%</td>
<td></td>
<td>42%</td>
</tr>
<tr>
<td>221 adult related vs unrelated paired analysis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Dahlke et al 2006</strong></td>
<td>84</td>
<td>43</td>
<td></td>
<td>45%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>84 pts, 43 in CR 1</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Marks et al 2008</strong></td>
<td>169</td>
<td></td>
<td></td>
<td>39%</td>
<td>20%</td>
<td>42%</td>
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<td>169 pts, in CR 1</td>
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<td></td>
</tr>
<tr>
<td><strong>Patel et al 2009</strong></td>
<td>55</td>
<td></td>
<td></td>
<td>59%</td>
<td>57%</td>
<td>19%</td>
</tr>
<tr>
<td>55 adults MUD median age 25</td>
<td></td>
<td></td>
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</tbody>
</table>
What if same patients had not been transplanted?

- Those with WBC >100×10^9/l → OS 21% at 5 yrs
- Those with t(4;11), low hypodiploidy, >5 cytogenetic abnormalities → 24%, 22%, 28% OS at 5 yrs
- Patients >35 yrs → 26% OS 5 yrs
- Those with multiple risk factors as above would probably have a survival even worse
- In all these subsets the observed DFS was superior after MUD transplant

Marks et al 2008
T cell depletion may facilitate MUD transplant - UK data (BSBMT)

Median age: 25 yrs
NRM: 19% at 5yrs
Gd III-IV acute GVHD: 7%
**Myeloablative allogeneic HSCT – not valuable over the age of 35 – 40yrs?**

Age > 35 years is the only factor that can be shown to be independently responsible for the increased TRM in the **high-risk** group.

<table>
<thead>
<tr>
<th>Age Category</th>
<th>5 year OS</th>
<th>No Donor</th>
<th>Donor</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 35 y, SR</td>
<td>52%</td>
<td>65%</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 35 y, SR</td>
<td>33%</td>
<td>43%</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 35 y, HR</td>
<td>40%</td>
<td>51%</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 35 y, HR</td>
<td>32.5%</td>
<td>14%</td>
<td>1.28</td>
<td></td>
</tr>
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</table>
Older patients do particularly badly with ALL OS by age, UKALL12/ECOG2993

Rowe et al 2005
## Reduced-intensity conditioning (RIC) for high-risk ALL

### CIBMTR Study of ALL in CR1 or CR2

<table>
<thead>
<tr>
<th></th>
<th>RIC (n=92)</th>
<th>vs</th>
<th>myeloablative (n=1421)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age yrs</strong></td>
<td>45</td>
<td></td>
<td>28 p= &lt; .0001</td>
</tr>
<tr>
<td><strong>OS @ 3 yrs, %</strong></td>
<td>38</td>
<td></td>
<td>43 p= 0.39</td>
</tr>
<tr>
<td><strong>TRM @ 3 yrs, %</strong></td>
<td>32</td>
<td></td>
<td>33 p= 0.86</td>
</tr>
<tr>
<td><strong>OS @ 4 yrs, %</strong></td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(all &gt; 55yrs)</td>
<td></td>
<td></td>
<td>Marks et al, ASH 2009-abstract 872</td>
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**ALSO**

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<td>(all &gt; 55yrs)</td>
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<td>Stadler et al ASH 2009-abstract 3388</td>
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Can MRD studies indicate which patients should have a transplant and which not?

- Vast majority of patients with adult ALL can have molecular targets identified

- MRD can be identified at different times in the disease and potentially identify different risk groups

- MRD relevance at any time point is dependent on specific prior therapy and possibly cannot be extrapolated from one protocol to another
MRD and risk adapted treatments in adult ALL n=223

- Probes obtained in 88%, single marker in 61%
- **Sensitivity level of $10^{-4}$ or higher in 94.2%**
- Risk-based data available in 78.9% of patients who completed first phase of treatment
- Loss of patients from MRD evaluation includes
  - absence of suitable marker
  - lack of adequate sampling
  - very high risk patients going direct to SCT
  - treatment related toxicity/death
  - early relapse

Bassan et al 2009
Outcomes strikingly improved in MRD$^{\text{neg}}$ patients versus MRD$^{\text{pos}}$

\[ P = .0000 \]
Outcomes strikingly improved in MRD$^{\text{neg}}$ patients versus MRD$^{\text{pos}}$

- BM relapse in patients with sensitive probes only 18.5\% in MRD$^{\text{neg}}$ patients
- Advantage for 36 MRD$^{\text{pos}}$ patients who had an allograft or hypercycle vs those who did not
- Don’t wait for data in high WBC patients, high risk T-Cell patients and those with poor risk cytogenetics

Bassan et al 2009
G-Mall MRD Studies

- **10%** have rapid decline of MRD to \(<10^{-4}\) and below limit of detection at d11 and d24: these have low relapse rate at 3 yrs and are **NOT** candidates for transplant.

- **90%** remain possible transplant candidates.

- **23%** have \(>10^{-4}\) until week 16 and have a 3 yr relapse rate of 94%; these **ARE** strong candidates for transplant.

*Raff et al 2007*  
*Goekbuget ASH 2009-abstract 90*
Superior efficacy of paediatric regimens?

- No randomised comparisons done

- Most convincing data are from concurrent adult and paediatric trials in which patients of same age group could have received either regimen

Fiere D 1990
Stock 2000
Boissel 2003
Testi 2004
de Bont 2004
Ramanajuchar 2005
Acute Lymphoblastic Leukaemia, Age 15-21
Paediatric vs ‘Adult’ Therapy

Seven Countries on Two Continents

Netherlands

- HO 8899 (Adult)
  Age 19-20 Years (N = 29)
  Age 15-18 Years (N = 44)

- CCG-1800 Series (Paediatric)
  Age 16-21 Years (N = 175)

- CALGB 8811-9511 (Adult)
  Age 16-20 Years (N = 103)

France

- FRALLE 93 (Pediatric)
  Age 15-20 Years (N = 77)

- LALA 94 (Adult)
  Age 15-20 Years (N = 100)

United Kingdom

- UKALLXII / E2993 (Adult)
  15-17 Years (N = 67)

Denmark and Italy

- HO 8899 (Adult)
  Age 19-20 Years (N = 29)

Seven Countries on Two Continents

after Litzow
Conclusion: The Eligibility Irony

• Will the high risk 25 – 45 yr old ALL in 1\textsuperscript{st} CR be the first group to benefit from a MUD allograft, and the even older patients to benefit from RIC?

• Will adolescents and young adults revert to chemotherapy rather than transplant?

• If both the above are true and come to pass, this will be the first scenario with fewer transplants for the young and more for the old!

• Finally, will MRD analysis reduce the use of allograft and resuscitate the use of autograft in this disease?
Of course, the evidence now is that not EVERY adult should have a transplant in CR – but a lot them should!
Current issues

1. How far can we go with paediatric protocols?
2. Will MRD negativity stop more allografts?
Final number will depend on:

1. What is the true upper age limit for adults to tolerate paediatric protocols

2. At what time point from diagnosis will the emergence of MRD negativity exclude transplant

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