Is FCR the standard therapy for older cancer patients with chronic lymphocytic leukemia?

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How to treat chronic lymphocytic leukaemia?

FCR
Fludarabine: 25mg m2 IV D1-3
Cyclophosphamide 250mg/m2 IV D1-D3
Rituximab: Cycle 1: 375 mg/m2, d 0
Cycles 2-6: 500 mg/m2, d 1

• FCR induces the highest remission rates ever reported

• FCR may change the natural course of CLL

• FCR should be the treatment of first choice in patients considered fit enough
Adverse events **CTC grade 3 and 4**

<table>
<thead>
<tr>
<th>Condition</th>
<th>FC</th>
<th>FCR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with $\geq 1$ grade 3/4 event</td>
<td>248 (62.9%)</td>
<td>309 (76.5%)</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Hematological toxicity</td>
<td>39.6%</td>
<td>55.7%</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21.0%</td>
<td>33.7%</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>12.1%</td>
<td>24.0%</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11.1%</td>
<td>7.4%</td>
<td>0.07</td>
</tr>
<tr>
<td>Anemia</td>
<td>6.8%</td>
<td>5.4%</td>
<td>0.42</td>
</tr>
<tr>
<td>Infection</td>
<td>21.5%</td>
<td>25.5%</td>
<td>0.18</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>0.5%</td>
<td>0.2%</td>
<td>0.55</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>0.0%</td>
<td>0.2%</td>
<td>0.32</td>
</tr>
</tbody>
</table>

How to treat chronic lymphocytic leukaemia?

• Only 11% of the patients were over 70 years

• All others may receive Chlorambucil

So, do we need something else?
Median age of patients in pivotal phase III CLL trials

Median age of diagnosis = 72

Professional experience required to “tailor” CLL therapy: characteristics at presentation

- Median age at diagnosis: 72 years\(^1\)
- Elderly patients may be fit or have comorbidities

### Mean no. of co-morbidities

\[ \text{Mean no. of co-morbidities} = \frac{\text{Total number of comorbidities}}{\text{Number of patients}} \]

<table>
<thead>
<tr>
<th>Age at CLL diagnosis (years)</th>
<th>Patients(^1) (%)</th>
<th>Mean comorbidities(^2) (all cancer types, n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 54</td>
<td>11</td>
<td>n/a</td>
</tr>
<tr>
<td>55–64</td>
<td>20</td>
<td>2.9</td>
</tr>
<tr>
<td>65–74</td>
<td>27</td>
<td>3.6</td>
</tr>
<tr>
<td>75+</td>
<td>43</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Who may not be eligible for fludarabine based therapy?

- Impaired renal function: debate exists: CrCl 30–70 ml/min mandates reduced dose
- Physically unfit (co morbidities, geriatric assessment)
- Risk for infection
Other chemoimmunotherapy combinations may allow therapy to be adapted to individual patients’ needs.

- **‘Go-go’**
  - Completely independent
  - No co-morbidity
  - Normal life expectancy
  → Aggressive chemotherapy

- **‘Slow-go’**
  - Some co-morbidity
  - Impaired organ function
  - Reduced performance status
  → Less aggressive approach

- **‘No-go’**
  - Severely handicapped
  - High co-morbidity
  - Reduced life expectancy
  → Palliative care

**Rituximab-FC is the standard of care**

**Where to draw the line?**

**What is the standard of care?**
### FC vs FC lite:
to target elderly/unfit CLL population

<table>
<thead>
<tr>
<th></th>
<th>Standard FC</th>
<th>FC-lite</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDACC 2005</strong></td>
<td>n=224</td>
<td>n=50</td>
</tr>
<tr>
<td><strong>Eichh. 2006</strong></td>
<td>n=180</td>
<td>n=26</td>
</tr>
<tr>
<td><strong>US IG 2007</strong></td>
<td>n=141</td>
<td>n=26</td>
</tr>
<tr>
<td><strong>CLL4 2007</strong></td>
<td>n=196</td>
<td>n=20</td>
</tr>
<tr>
<td><strong>Cazin 2008</strong></td>
<td>n=76</td>
<td></td>
</tr>
<tr>
<td><strong>Foon 2009</strong></td>
<td>n=50</td>
<td></td>
</tr>
<tr>
<td><strong>Forconi 2008</strong></td>
<td>n=26</td>
<td></td>
</tr>
<tr>
<td><strong>Marotta 2000</strong></td>
<td>n=20</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Age (y)</strong></th>
<th>57</th>
<th>58</th>
<th>61</th>
<th>65</th>
<th>57</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>42-64</td>
<td>39-86</td>
<td>40-86</td>
<td>37-66</td>
<td>36-84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Rai 0-II</strong></th>
<th>67%</th>
<th>7%</th>
<th>54%</th>
<th>25%</th>
<th>0%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Min R funct</strong></td>
<td>2 mg/dL</td>
<td>NA</td>
<td>40 ml/min</td>
<td>NA</td>
<td>« good »</td>
</tr>
<tr>
<td><strong>CIRS</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

| **Median age:** | FC standard 59.6 y vs FC lite 67.6 y |
# CLL trials in the elderly and/or unfit

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>CR (%)</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCLLSG CLL5</td>
<td>Chlorambucil Fludarabine</td>
<td>100</td>
<td>0</td>
<td>51</td>
<td>18</td>
<td>Eichhorst et al, 2009 65 – 80 years of age No sig diff in PFS or OS Median age 70-71 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>93</td>
<td>7</td>
<td>72</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Multicentre phase III</td>
<td>Chlorambucil Bendamustine</td>
<td>157</td>
<td>2</td>
<td>31</td>
<td>8.3</td>
<td>Knauf et al, 2009 Median age 64 years No sig diff in ORR in &lt;65 and &gt;65 year olds (BEN 71.6% vs 63.5%, p&gt;0.3; CLB 28.4% vs 32.5%, p&gt;0.06) PFS not influenced by age &gt;65 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>162</td>
<td>31</td>
<td>68</td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td>CLL208</td>
<td>Chlorambucil + Rituximab</td>
<td>100</td>
<td>9</td>
<td>82</td>
<td>23.5</td>
<td>Hillmen et al, 2010 Median age 70 years (range 43–86)</td>
</tr>
<tr>
<td>Ph II</td>
<td>CLB-R +/- R maintenance*</td>
<td>54</td>
<td>20.4</td>
<td>81.4</td>
<td>NR</td>
<td>Foa et al, 2010 Median age 70.5 years (range 61–84)</td>
</tr>
</tbody>
</table>

NR = not reported  * Interim analysis measuring tumour response at end of induction phase on ITT
GCLLSG CLL5: Phase III Trial of Fludarabine vs Chlorambucil in Elderly (>65yo) CLL

No significant difference seen in either OS or PFS between arms

Is chlorambucil an effective therapy for elderly/unfit patients with CLL?

- Outcome varies by dose and duration of treatment
  - Higher doses and longer duration of therapy lead to:
    - Overall response rates >70% and CR rates 5-10%
    - Median PFS ~18 months in front-line CLL
    - Median overall survival >5 years
- Can we improve on chlorambucil?
  - alternative chemotherapy?
  - addition of monoclonal antibodies?
European Phase III Front-line CLL Study: progression-free survival

Median age ~ 63 years old!

Median PFS: bendamustine 21.6 months; chlorambucil 8.3 months; p<0.0001

Knauf W et al. J Clin Oncol 2009;27:4378–84
European Phase III ‘Intergroup’ CLL Study: sub-analysis by age

Progression-free survival by treatment group and age

- Age <65 years – Bendamustine (n=87; median=20.9)
- Age <65 years – Chlorambucil (n=68; median=8.7)
- Age ≥65 years – Bendamustine (n=74; median=21.3)
- Age ≥65 years – Chlorambucil (n=79; median=9.4)

Knauf W et al. Blood 2009;114: Abs 2367 and accompanying poster
Relative PFS for chlorambucil and bendamustine

LRF CLL4 Trial

European Phase III Trial

Phase I study in patients with MM and renal disease: bendamustine pharmacokinetics

Bendamustine concentration (ng/mL)

* Each patient received 120mg/m² d1+2 q4w

R-chlorambucil in first-line CLL: Study design

- **Final analysis of UK CLL208 study**
  - Single arm, Phase II study
  - R-chlorambucil for first-line CLL patients (N = 100)

- **Primary endpoint: safety**
  - Efficacy measures (response rate, PFS) included as secondary endpoints

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- **MabThera:** 500 mg/m² (375 mg/m² cycle 1)
  - Chlorambucil: 10 mg/m²/day for 7 days

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Further 6 cycles chlorambucil alone if patient not in CR and continuing to respond
CLL208: Response rates

- **SD/PD**: 17%
- **Missing**: 3%
- **CR**: 12%
- **PR**: 68%

**ORR=80%**
95% CI 70.8–87.3

**Median PFS**: 23 months

No patients had an MRD negative remission

Hillmen P, presented at ASH 2010
## Matched-pair analysis: Response rates

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>CR</th>
<th>ORR</th>
<th>SD/PD</th>
<th>Not evaluable</th>
<th>95% CI for % of patients achieving at least a PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-chlorambucil</td>
<td>100</td>
<td>12%</td>
<td>80%</td>
<td>17%</td>
<td>3%</td>
<td>[70.8, 87.3]</td>
</tr>
<tr>
<td>Chlorambucil¹</td>
<td>200</td>
<td>6%</td>
<td>66%</td>
<td>30%</td>
<td>4%</td>
<td>[59.0, 72.5]</td>
</tr>
</tbody>
</table>

Median PFS: 18months

Hillmen P, presented at ASH 2010

New monoclonal antibodies

GA101
- CD20 monoclonal
- Glyco-engineered
- Humanized, type II

Ofatumumab
- CD20 monoclonal
- Humanized, type I

* Amino acids depicted in red or yellow are involved in the binding of ofatumumab or rituximab, respectively, as determined by X-ray crystallography. Numbers in the extracellular loop reflect amino acids involved in the binding of ofatumumab (137, 143, 190, and 211) and rituximab (128, 172) as determined in competitive binding studies.
## Ongoing CLL studies in the unfit and/or elderly

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Previous therapy</th>
<th>Treatment</th>
<th>Recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MaBLe (Roche)</td>
<td>IIIb</td>
<td>No and yes</td>
<td>Chlorambucil-R, Bendamustine-R</td>
<td>Ongoing</td>
</tr>
<tr>
<td>CLL-11 (Roche)</td>
<td>III</td>
<td>No</td>
<td>Chlorambucil-R, Chlorambucil-GA101</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Complement-1 (GSK)</td>
<td>III</td>
<td>No</td>
<td>Chlorambucil</td>
<td>Ongoing</td>
</tr>
<tr>
<td>RIAltO (GSK)</td>
<td>III</td>
<td>No</td>
<td>Chlorambucil-O, Bendamustine-O</td>
<td>Planned</td>
</tr>
<tr>
<td>Origin (Celgene)</td>
<td>III</td>
<td>No</td>
<td>Chlorambucil, Lenalidomide</td>
<td>Ongoing</td>
</tr>
<tr>
<td>GOELAMS and FCGCLL/WM</td>
<td>III</td>
<td>No</td>
<td>FCR +/- R maintenance</td>
<td>Ongoing</td>
</tr>
<tr>
<td>GOELAMS and FCGCLL/WM</td>
<td>II</td>
<td>No</td>
<td>Chlorambucil, Fludarabine+ cyclophosphamide lite</td>
<td>Planned</td>
</tr>
</tbody>
</table>


Conclusion: CLL in Older Patients, a Problem in Search of Solutions

- FCR improves survival and is the “gold-standard” for all patients considered fit enough for therapy
- Evaluation of comorbidities and geriatric assessment
- We need a validated, simple-to-use CLL comorbidity and fitness scale
- The most appropriate therapy for those unfit for FCR could be:
  - Chlorambucil monotherapy (appropriate dosing!!)
- Combinations that are being tested include:
  - Chlorambucil + anti-CD20 (Rituximab, ofatumumab, GA-101)
  - Alternative chemotherapy Bendamustine + anti CD20
  - FCR lite
Fitness status and treatment selection in front-line CLL

MRD-/OS  Durable remission  Symptom control/palliation

Very fit  FCR-lite?  ?  Very unfit

FCR  B +R  Clb-R?  Ofatumumab

Chlorambucil +/- R
Geriatric Oncology: Cancer in Senior Adults

11th Meeting of the International Society of Geriatric Oncology
November 3–5, 2011
Paris, France

For more information, please visit: www.siog.org