Chronic lymphocytic leukemia is eradication feasible and worthwhile?

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Minimal residual disease (MRD) negativity in CLL

Is MRD homogeneously defined in the literature?

Is there any advantage in treating CLL until MRD eradication?

Is MRD eradication a realistic goal in most CLL?

Is MRD eradication a surrogate marker of biologically favourable CLL?

What is the clinical cost of MRD eradication?
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Technical approaches for MRD detection in CLL are heterogeneous

<table>
<thead>
<tr>
<th></th>
<th>Dual color flow cytometry</th>
<th>Consensus-primer IgH PCR</th>
<th>Multiparametric flow cytometry</th>
<th>RQ-ASO IgH PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Applicability</strong></td>
<td>CD5+/CD19+ cells</td>
<td>Amplifiable IgH gene R</td>
<td>Typical phenotype</td>
<td>Amplifiable IgH gene R</td>
</tr>
<tr>
<td><strong>Limit of detection</strong></td>
<td>1% - 0.1%</td>
<td>1% - 0.1%</td>
<td>0.01%</td>
<td>0.001%</td>
</tr>
<tr>
<td><strong>Advantage</strong></td>
<td>Low cost</td>
<td>Low cost</td>
<td>Fast</td>
<td>Sensitive</td>
</tr>
<tr>
<td><strong>Disadvantage</strong></td>
<td>Usually uninformative</td>
<td>Least informative assay</td>
<td>Fresh material necessary</td>
<td>Cost and time (needs patient specific primers)</td>
</tr>
</tbody>
</table>
Sensitivity of technical approaches for MRD detection in CLL

- Dual color flow cytometry
- Consensus-primer IgH PCR
- Multiparametric flow cytometry
- RQ-ASO IgH PCR

DIAGNOSIS

- 100%
- 10%
- 1%
- 0.1%
- 0.01%
- 0.001%
Technical approaches for MRD detection in CLL: caveat heterogeneity among centers and among trials!

Heterogeneity for MRD evaluation in CLL:

- in methods utilized
- in sensitivity threshold
- among clinical trials
- in the clinical practice
Technical approaches for MRD detection in CLL: caveat heterogeneity among centers and among trials!

Heterogeneity for MRD evaluation in CLL:

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- in sensitivity threshold
- among clinical trials
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Despite current limitations, it should be acknowledged that CLL MRD investigators are making efforts toward MRD standardization
Threshold for defining MRD eradication according to IWCLL-NCI guidelines

- Dual color flow cytometry
- Consensus-primer IgH PCR
- Multiparametric flow cytometry
- RQ-ASO IgH PCR

IWCLL – NCI guidelines 2008
The deeper is the response, the longer is time to progression, independent of the treatment strategy.

Bottcher S, ASH 2008 (CLL 8 trial)
Despite efforts from the IWCLL-NCI guidelines for standardizing sensitivity, MRD in CLL is far from reaching the standardization of MRD in CML:

- lack of standardized technique
- lack of standardized timing
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Algorithm for the management of CLL patients

<table>
<thead>
<tr>
<th>Young patients group</th>
<th>Elderly patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td><strong>Group 2</strong></td>
</tr>
<tr>
<td>Completely independent in ADL</td>
<td>Somewhat impaired</td>
</tr>
<tr>
<td>No comorbidity</td>
<td></td>
</tr>
<tr>
<td>Normal age-matched life expectancy</td>
<td></td>
</tr>
</tbody>
</table>

*“Go go”*
- Intensive therapy: FCR, R-FCM, Allogenic stem cells transplantation
- Long-lasting remission and cure

*“Go go”*
- Intensive therapy: FC, FCR, R-FCM
- Long-lasting remission

*“Slow go”*
- Mild therapy: CLB, alemtuzumab F-mono
- Control of symptoms

*“No go”*
- Palliative Care
MRD-negative CR can be currently obtained only with intensive treatments

Keating, JCO 2005
Hillmen, JCO 2007
Bosch, CCR 2008
Bosch, JCO 2009
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Two different settings:

• induction therapy

• consolidation / maintenance therapy
Infections in different CLL chemotherapeutic regimens (induction therapy)

Keating, JCO 2005
Hillmen, JCO 2007
Bosch, CCR 2008
Bosch, JCO 2009
Strategies for tailoring MRD eradication: consolidation with monoclonal antibodies

Fludarabine $25\text{mg/m}^2$  
From day 1 to day 5 of each cycle

Alemtuzumab 30mg  
Three times per week (first week dose escalation from 3mg to 30mg)

Trial closed for unacceptable toxicity

Wendtner et al. Leukemia, 2004
## ALEMTUZUMAB: CONSOLIDATION / MRD ERADICATION

*(Montillo et al., J Clin Oncol 24: 2337, 2006)*

<table>
<thead>
<tr>
<th>After Fluda</th>
<th>Response to Alemtuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>12 (35%)</td>
</tr>
<tr>
<td>PRn</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>PR</td>
<td>15 (44%)</td>
</tr>
<tr>
<td>Total</td>
<td>27 (79.4%)</td>
</tr>
</tbody>
</table>

| Poly IgH | 0% | 19 (56%) |
Fludarabine based + alemtuzumab or rituximab consolidation in CLL

- % MRD-negative pre-consolidation therapy
- % MRD-negative post-consolidation therapy
- Patients who did not start consolidation therapy
- Patients who did not complete consolidation therapy

Lin, JCO 2010
Lamanna, JCO 2009

Lin, JCO 2010
Hainsworth, BJH 2008
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**GOLDEN AGE of NEW CLL PROGNOSTICATORS**

**TP53 mutation**

C13397T > Arg213STOP

**Telomere length**

<table>
<thead>
<tr>
<th>Case</th>
<th>bp</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2830</td>
</tr>
</tbody>
</table>

**CD49d expression**

**IGH translocation**

**Host SNPs**

<table>
<thead>
<tr>
<th>VDJ</th>
<th>CDR3 aa sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>V4-39</td>
<td>IGYSSWYGGSNWFDP</td>
</tr>
<tr>
<td>V4-39</td>
<td>SR----------E----------</td>
</tr>
<tr>
<td>V4-39</td>
<td>NS----------FR-YS------</td>
</tr>
<tr>
<td>V4-39</td>
<td>HL----------AA--------</td>
</tr>
</tbody>
</table>
A single study (FCR) tested the relationship between MRD and biological predictors.

The proportion of patients achieving MRD-negative CR were:

- 57% in IGHV unmutated
- 67% in IGHV mutated

Caveat definition of MRD-negativity: <1% CLL cells detected by dual color flow cytometry

Lin et al. Blood, 2009
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Few clinical trials in CLL include MRD evaluation

PubMed research criteria:

- Keyword: “chronic lymphocytic leukemia”
- Limits: → date: from 2001/01/01 to 2010/08/01
  → journals: NEJM, Lancet, JCO, Blood
  → type of article: clinical trial

Total no. of clinical trials: 112

Clinical trials including MRD assessment: 11

Clinical trials including MRD eradication as a primary end-point: 0
Methods to monitor clinical response and to detect MRD in CLL clinical trials

- Dual color flow cytometry
- Consensus-primer IgH PCR
- Multiparametric flow cytometry
- RQ-ASO IgH PCR

Number of trials:
- No. 3 trials: Dual color flow cytometry, Consensus-primer IgH PCR
- No. 5 trials: Multiparametric flow cytometry
- No. 0 trials: RQ-ASO IgH PCR
MRD-negativity achievement can be considered curative in CLL only in allo-transplanted patients.

MRD-negativity curve reaches a plateau only in patients undergoing allogeneic stem cells transplantation.

Bottcher S, ASH 2008 (CLL 8 trial)
Dreger, Blood 2010
Minimal residual disease (MRD) negativity in CLL: A provocative question

Is MRD homogeneously defined in the literature?

Is MRD eradication a realistic goal in most CLL?

Are current MRD targets (BM, PB) the best possible targets?

Is there any advantage in treating CLL until MRD eradication?

What is the clinical cost of MRD eradication?

Is MRD eradication a surrogate marker of biologically favourable CLL?
The proliferation centers of CLL reside predominantly in lymph nodes.

BM and PB may not fully reflect the events taking place in proliferation centers.