Integrating PET and MRD in follicular lymphoma

Stefano Luminari, MD
Medical Oncology
Università di Modena e Reggio Emilia, Modena Italy
Current concepts in FL

• The identification patients at high risk of relapse is a critical goal of modern research in oncohematology and FL.

• Individual risk of relapse is estimated:
  – Before therapy: Prognostic scores (FLIPI and FLIP2), biomarkers, SNPs, GEP mol. signatures
  – After therapy: FDG-PET, CT-scan, MRD
Response assessment in FL

PET:
• Has the highest prognostic impact on PFS and OS Trotman et al Lancet Hematol 2014 Vol1 n1 p1
• Is now recommended for staging and response assessment in updated criteria Cheson et al JCO 2014

CT:
• Is difficult to assess (SPD) Cheson et al JCO 2007
• Has limited capacity to assess extranodal disease
• Has lower prognostic impact than FDG-PET for PFS and none for OS Trotman et al Lancet Hematol 2014 Vol1 p1 n1

Molecular analysis:
• Has the highest sensitivity among available methods in CLL and MCL
• FL are an excellent model due to t(14;18) chr. Translocation Gribben et al. Blood 1994
Schematic representation of t(14;18) chromosomal translocation

Germline BCL-2 chr 18q21

Genomic DNA Chr 14q+

Germline BCL-2 chr 18q21:
- 3% MBR
- 81% MBR
- 16% MCR

Genomic DNA Chr 14q+:
- Chromosomal translocation involving Chr 14 and Chr 18
- 225 kb

First PCR
- t(14;18)+
- t(14;18)-
- cDNA

Nested PCR
- t(14;18)+
- t(14;18)-
- cDNA
MRD may indicate depth of remission and predict relapse

Detection limit of cytology/CT scan$^1$: $10^{-1}$–$10^{-2}$

Detection limits of flow cytometry and PCR techniques$^3$: $10^{-4}$–$10^{-6}$

Still in remission and MRD negative

Prognostic role of Minimal residual disease and beta2-microglobulin in patients with FL

Minimal residual disease assessment of the GITMO randomized trial comparing R-CHOP vs R-HDS in high risk FL patients

Effect of MRD by response status and treatment group.

Current problems with MRD in FL

• No universal marker (t(14;18) available in~60%)
• Needs BM aspirate
• Compartment phenomenon (BM, PB and LN)
• Timing of MRD is uncertain
• No clear understanding of very low concentration of FL cells (false positives)
• No study has ever correlated MRD and FDG PET
 PET RESPONSE AND MINIMAL RESIDUAL DISEASE IMPACT ON PROGRESSION-FREE SURVIVAL IN PATIENTS WITH FOLLICULAR LYMPHOMA

**Poster B10**

- Pts with centrally reviewed PET (5PS x3 with liver cutoff) (FOLL05; N=79)
- Baseline search for t(14;18)*(N=68)
- MRD analysis* on postinduction BM sample (N=41)

**Table 1. Distribution of cases according to piPET and MRD**

<table>
<thead>
<tr>
<th></th>
<th>MRD -</th>
<th>MRD+</th>
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<tbody>
<tr>
<td>piPET-</td>
<td>28 (68%)</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>piPET+</td>
<td>2 (5%)</td>
<td>3 (7%)</td>
</tr>
</tbody>
</table>

\[ P = 0.110 \ K=.249(FAIR) \]

**Figure 1. PFS according to piPET**

- piPET- (score 0-3), N=36
- piPET+ (score 4-5), N=5

**Figure 2. PFS according to MRD**

- MRD-, N=30
- MRD+, N=11

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95%CI</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>piPET+</td>
<td>3.62</td>
<td>1.15-11.4</td>
<td>.028</td>
</tr>
<tr>
<td>MRD+</td>
<td>2.54</td>
<td>0.96-6.72</td>
<td>.060</td>
</tr>
</tbody>
</table>

(*) nested PCR for t(14;18) ch. translocation. All tests were performed within the Fil MRD network (Galimberti et al. Submitted)
PET response and minimal residual disease impact on progression-free survival in patients with follicular lymphoma.
FOLL12 TRIAL DESIGN (EudraCT Number: 2012-003170-60)
1° line, stage II–IV, FL (P.I. M. Federico)

FOLLICULAR NHL
Grade I–II–IIIa
Age 18–75
Stage II–IV
Active disease
FLIPI2≥1
Preliminary analysis of PET and t(14;18) from the FOLL12 clinical trial

- 193 patients enrolled at 8/2014
- All baseline and restaging PET were centralized and reviewed at the end of induction therapy (Widen)
- Molecular analysis was performed timely at registration and at the end of therapy* by FIL MRD network.
- 118 FL had a detectable t(14;18)(61%) at time of diagnosis (LN, BM or PB)
- Preliminary results are available for
  - Staging PET and qualitative molecular analysis (N=118)*
  - Staging PET and quantitative molecular analysis (N=83)*
  - Not enough data for restaging PET and MRD analysis

(*) nested PCR for t(14;18) ch. translocation. All test were performed within the FIL MRD network
## Baseline characteristics (n=118)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>%pend.</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM (IHC) +</td>
<td>118</td>
<td>-</td>
<td>67 (57)</td>
</tr>
<tr>
<td>PET bone +</td>
<td>118</td>
<td>-</td>
<td>40 (34)</td>
</tr>
<tr>
<td>t(14;18) BM qual +</td>
<td>118</td>
<td>-</td>
<td>77 (65)</td>
</tr>
<tr>
<td>t(14;18) PB qual +</td>
<td>111</td>
<td>6</td>
<td>66 (59)</td>
</tr>
<tr>
<td>t(14;18) + (BM or PB +)</td>
<td>118</td>
<td>-</td>
<td>79 (67)</td>
</tr>
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</table>

**Median (2.5-97.5° )**

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<tbody>
<tr>
<td>t(14;18) BM quant *</td>
<td>83</td>
<td>30</td>
<td>-2.30 (-8; 0.270)</td>
</tr>
<tr>
<td>t(14;18) PB quant *</td>
<td>75</td>
<td>36</td>
<td>-2.40 (-8; 0.130)</td>
</tr>
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</table>

* Quantitative bcl2 MRD in Log10
PET and t(14;18) qualitative test as surrogates for BM involvement in FL

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>ACC.</th>
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<tbody>
<tr>
<td>FDG-PET (bone)</td>
<td>0.45</td>
<td>0.8</td>
<td>0.75</td>
<td>0.53</td>
<td>0.6</td>
</tr>
<tr>
<td>t(14;18) (BM)</td>
<td>0.72</td>
<td>0.39</td>
<td>0.61</td>
<td>0.51</td>
<td>0.58</td>
</tr>
<tr>
<td>PET and t(14;18)</td>
<td>0.62</td>
<td>0.58</td>
<td>0.81</td>
<td>0.35</td>
<td>0.61</td>
</tr>
</tbody>
</table>
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Conclusions

• Both FDG-PET and t(14;18) analysis are good techniques to study FL and there is a rationale to combine them.

• Very preliminary results suggest that it is useful to integrate PET and MRD analysis (staging and restaging).

• FOLL12 trial will provide new data on PET and MRD correlation.

• In the future new molecular techniques (NGS) will probably overcome some of the current limitations of MRD analysis in FL and other NHL.
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