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Can We Identify High-Risk Follicular Lymphoma Before Starting Treatment?

Robert Kridel, MD, MPH, PhD
Disclosure information

- I have the following relevant financial relationships to disclose:
  - Consultant for: N/A
  - Speaker’s Bureau for: N/A
  - Grant/Research support from: Gilead Sciences
  - Stockholder in: N/A
  - Honoraria from: N/A
  - Employee of: N/A

- I will not discuss off label use or investigational use in my presentation
Overview

• Introduction

• Genomic basis of 2 scenarios associated with adverse outcome
  • Transformation to aggressive histology
  • Early progression

• Risk prediction:
  • Clinical risk scores (FLIPI, FLIPI-2, PRIMA-PI)
  • PET scan at baseline
  • Genomic biomarkers (TP53, m7-FLIPI, 23 gene predictor)
Clinical course is highly variable, and the heterogeneity of pathogenetic mechanisms.
Early steps of FL pathogenesis

Pre-B cell t(14;18)

Bone Marrow

KMT2D CREBBP?

In situ follicular neoplasia

Re-entry into the germinal center

t(14;18)+ B cells "FL-like cell"

FL

Secondary lymphoid organs

Accumulation of secondary events and progression to disease

Pre-clinical

Clinical

Lackraj, Goswami and Kridel, BPRCH, 2018
Re-education of the tumour microenvironment

- **Support from microenvironment**
  - *TNFRSF14* mutations → lymphoid stroma activation (Boice et al, Cell, 2016)

- **Escape from immune surveillance**
  - *CREBBP* mutations → down-regulation of MHC class II (Green et al, PNAS, 2015)
  - *B2M* mutations → loss of MHC class I, reduced CD8+ T-cell infiltrate (Kridel and Chan et al, PLOS Med, 2016)
Intratumoral heterogeneity

Peter Nowell, Science, 1976

Araf et al, Leukemia, 2018
Can circulating tumour DNA analysis detect relevant mutations, irrespective of spatial heterogeneity?

Scherer et al, Science Translational Medicine, 2016
Transformation is associated with poor survival

10-year cumulative incidence = 7.7%

Federico et al, Lancet Haematology, 2018
Transformation is associated with poor survival

- Patients randomly assigned (N = 1,018)
  - Histologic review: DLBCL (n = 1)
    - No relapse (n = 554)
    - Relapse (n = 463)
      - No biopsy (n = 269; 58%)
      - Biopsy (n = 194; 42%)
        - Follicular lymphoma histology (n = 154; 79.4%)
        - Histologic transformation (n = 40; 20.6%)

Sarkozy et al, JCO, 2016
Genetics of transformed lymphoma

Sequencing of targeted gene panel.
N=128 follicular lymphoma samples; n=149 transformed lymphoma samples. N=118 paired.
Genetics of transformed lymphoma

- Defective DNA damage response ($TP53$)
- Increased proliferation ($MYC$ translocations, $CCND3$)
- Loss of confinement within germinal centre ($GNA13$, $P2RY8$, $S1PR2$)
- Escape from immune surveillance ($B2M$)

Kridel and Chan et al. PLOS Medicine 2016
The expression levels of microenvironment-associated genes change upon transformation
Clonal dynamics of transformation

A

B

Diagnosis of FL

TFL

Cancer cell fraction: TFL

0.00 0.25 0.50 0.75 1.00

0.00 0.25 0.50 0.75 1.00

Cancer cell fraction: FL

extinguished FL mutations

ancestral mutations

emerging TFL mutations

FL clones

TFL clones

Kridel and Chan et al. PLOS Medicine 2016
Early progression after R-chemotherapy is associated with adverse outcome

**Princess Margaret/Sunnybrook**
132 patients, R-CVP/R-CHOP
22 (16.7%) early progression, incl. 8 transformation

**BC Cancer**
296 patients, BR
35 (12%) early progression, incl. 28 transformation

Mozessohn et al, Leuk Lymph, 2014
Freeman et al, ASH 2018
Genetics of early progression

Sequencing of targeted gene panel.
Outcome extremes: early progressors (n=41) and late/never progressors (n=84).
Genetics of early progression

- Defective DNA damage response (*TP53*)
- Escape from immune surveillance (*B2M*)
- *FAS, BTG1, XBP1, …*

*Kridel and Chan et al. PLOS Medicine 2016*
Clonal dynamics of early progression

Kridel and Chan et al. PLOS Medicine 2016
Clinical risk scores

**FLIPI**
- Age > 60
- Hemoglobin < 120
- Ann Arbor III-IV
- Number of nodal areas > 4
- LDH > normal

**FLIPI-2**
- Age > 60
- Hemoglobin < 120
- \(\beta_2\) microglobulin > normal
- Largest LN > 6 cm
- Bone marrow involved

**PRIMA-PI**
- \(\beta_2\) microglobulin > 3 mg/L
- Bone marrow involved

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**Solal-Céligny et al, Blood, 2004**

**Federico et al, JCO, 2009**

**Bachy et al, Blood, 2018**
## Clinical risk scores

### FLIPI

- **Survival probability**
- **Progression free survival (months)**
- **No of events**
  - Low: 83
  - Int: 187
  - High: 293

### FLIPI2

- **Survival probability**
- **Progression free survival (months)**
- **No of events**
  - Low: 20
  - Int: 276
  - High: 270

### PRIMA-PI

- **Survival probability**
- **Progression free survival (months)**
- **No of events**
  - Low: 124
  - Int: 172
  - High: 213

### Training cohort (PRIMA)

<table>
<thead>
<tr>
<th></th>
<th>FLIPI</th>
<th>PRIMA-PI</th>
<th>FLIPI2</th>
<th>β₂m+LDH</th>
<th>FLIPI</th>
<th>PRIMA-PI</th>
<th>β₂m+LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-rank χ²</td>
<td>45.64</td>
<td>81.96</td>
<td>54.12</td>
<td>41.23</td>
<td>27.17</td>
<td>29.47</td>
<td>19.39</td>
</tr>
<tr>
<td>CPE (±SE)</td>
<td>0.577 (±0.011)</td>
<td>0.604 (±0.011)</td>
<td>0.577 (±0.010)</td>
<td>0.572 (±0.011)</td>
<td>0.605 (±0.020)</td>
<td>0.606 (±0.019)</td>
<td>0.577 (±0.017)</td>
</tr>
<tr>
<td>NRI (±SE)</td>
<td>ref</td>
<td>+36.7% (±6.1%)</td>
<td>+24.7% (±5.8%)</td>
<td>-1.3% (±5.9%)</td>
<td>ref</td>
<td>+3.5% (±8.7%)</td>
<td>-7.1% (±9.8%)</td>
</tr>
</tbody>
</table>

### Validation cohort (FL2000+MER) *

* Bachy et al, Blood, 2018
Baseline PET scan: total metabolic tumour volume

N=185 patients from 3 prospective trials

R-chemo induction

The specificity of high TMTV for progression within 2 years was 78%; the sensitivity was 56%.

Meignan et al, JCO, 2016
Baseline PET scan: SUVmean dominant mass

N=182 patients from E2408 trial

BR induction

Baratto et al, ASH, 2018
Genetic alterations as prognostic biomarkers: example of *TP53*

**LLMPP**
*TP53* mutated 12/185 = 6%

**GLSG2000**
*TP53* mutated 8/143 = 5%

Pastore et al. Lancet Oncol 2015
m7-FLIPI: a clinico-genetic risk model
multivariate, parsimonious, robust

Pastore et al. Lancet Oncol 2015
High-risk FLIPI patients that are actually low risk
→ non-high risk m7-FLIPI

Pastore et al. Lancet Oncol 2015
Failure-free survival by m7-FLIPI risk score

Training cohort
Clinical trial (GLSG)
n=151

Validation cohort
Population-based (BCCA)
n=107

Pastore et al. Lancet Oncol 2015
Predicting early progression ("POD24")

A

<table>
<thead>
<tr>
<th>FLIPI</th>
<th>low/inter-risk</th>
<th>high-risk</th>
</tr>
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<tbody>
<tr>
<td><strong>GLSG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR = 4.6 (p=0.0059)</td>
<td>56%</td>
<td>44%</td>
</tr>
<tr>
<td>POD24</td>
<td>no POD24</td>
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<tr>
<th>m7-FLIPI</th>
<th>low-risk</th>
<th>high-risk</th>
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<tbody>
<tr>
<td><strong>BCCA</strong></td>
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</tr>
<tr>
<td>OR = 3.2 (p=0.035)</td>
<td>58%</td>
<td>42%</td>
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<tr>
<td>POD24</td>
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<tr>
<th>m7-FLIPI</th>
<th>low-risk</th>
<th>high-risk</th>
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<tbody>
<tr>
<td><strong>GLSG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR = 5.8 (p=0.00031)</td>
<td>21%</td>
<td>79%</td>
</tr>
<tr>
<td>POD24</td>
<td>no POD24</td>
<td>no POD24</td>
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<tr>
<th>m7-FLIPI</th>
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<th>high-risk</th>
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<tbody>
<tr>
<td><strong>BCCA</strong></td>
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</tr>
<tr>
<td>OR = 4.8 (p=0.0052)</td>
<td>86%</td>
<td>14%</td>
</tr>
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<td>POD24</td>
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C

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<thead>
<tr>
<th>POD24-PI</th>
<th>low-risk</th>
<th>high-risk</th>
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<tbody>
<tr>
<td><strong>GLSG</strong></td>
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</tr>
<tr>
<td>OR = 7.3 (p&lt;0.001)</td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>POD24</td>
<td>no POD24</td>
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<tr>
<th>POD24-PI</th>
<th>low-risk</th>
<th>high-risk</th>
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</thead>
<tbody>
<tr>
<td><strong>BCCA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR = 4.3 (p=0.0051)</td>
<td>73%</td>
<td>27%</td>
</tr>
<tr>
<td>POD24</td>
<td>no POD24</td>
<td>no POD24</td>
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</tbody>
</table>

EZH2 wild-type status combined with high-risk FLIPI is a poor-risk scenario

Pastore et al. Lancet Oncol 2015
FOXP1 is down-regulated in EZH2-mutated FL

Mottok et al, Blood, 2018
High levels of FOXP1 expression are associated with poor FFS

Mottok et al, Blood, 2018
Pathways enriched in FOXP1-high expressors

Mottok et al, Blood, 2018
Gene expression of 23 genes predicts progression

Trained in samples from PRIMA trial.
Genes associated with outcome identified initially using Affymetrix microarrays.
Transposed to NanoString platform.
Gene expression of 23 genes predicts progression

Huet et al, Lancet Oncol, 2018
Validation of 23 gene model in BC Cancer cases (treated with R-CVP, +/- R maintenance)

Silva et al, Haematologica, 2019
Identification of 2 groups of patients

Silva et al, Haematologica, 2019
Association of poor risk gene sets from Huet et al. with FOXP1 expression

Silva et al, Haematologica, 2019
Conclusions

Clinical, radiological and genetic risk tools allow to identify patients who are at higher risk of poor outcome when exposed to R-chemo

Individualization of therapy based on risk makes sense if we can target biology that underlies poor-risk disease

Potential for biology-adapted rather than risk-adapted therapy

Intratumoral heterogeneity remains a challenge

Most risk models are based on small patient cohorts and do not leverage the power of machine learning approaches to optimize model performance
Thank you for your attention

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Germany:
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Anja Mottok
Oliver Weigert
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