Quantitative pre-treatment PET in Follicular Lymphoma

Preliminary data from the PET Folliculaire Trial

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How we used to look at FL

1. Indolent B-cell lymphoma of mostly elderly
2. Watch and wait an accepted approach
3. Good response to treatment
4. Constant relapses
5. Shorter duration of subsequent remissions
6. Risk of transformation into aggressive NHL
The changing face of FL in recent years

1. Common lymphoma – and >60yrs is not so old!
2. Pre-treatment prognostic indices – assist in triaging who to W+W
3. Excellent response to immuno-chemotherapy
4. Duration of remissions prolonged by maintenance Rituximab
5. Risk of transformation into aggressive NHL
6. Death from lymphoma becoming a later event
Follicular lymphoma: Recognised Heterogeneity

Histology
• Grade 1-3a correlates poorly with outcome
• Poor reproducibility 3a vs. 3b (transformation)

Heterogeneity in patient outcomes
• FLIPI (>4 Nodal areas / LDH / Age>60 / Stage III-IV / Hb<12)  
  – 5yr OS 91 vs. 53%, Low vs. High risk
• FLIPI2 (B2M>ULN / LoDLIN>6cm / BMI / Hb<12 / Age>60)  
  – 3yr PFS 89 vs. 57%
  – 3yr OS 99 vs. 82%
Can FDG-PET add clinically useful information to initial staging?

- Almost universally but not uniformly FDG avid

- Poor correlation of $SUV_{max}$ with histologic grade
  Wohrer 2006, Karam 2006

- No clear cut-off defines transformation
  $SUV_{max} < 11.7 = \text{indolent}, \ S UV_{ max } > 17 = \text{transformation}$
  Bodet-Milin 2008
PET-Folliculaire:
Pre-treatment $SUV_{\text{max}} > 13.7 (>75^{\text{th}} \text{percentile})$ & FLIPI in two classes

Prospective GELA/LYSA study
• $n = 109$
• high tumour burden FL
• 6 R-CHOP+2 Rituximab

Baseline SUV max
• mean = 11.4
• range 3.3-34

Dupuis J et al, PET-Folliculaire study
Postinduction PET
Deauville score (5PS) ≥4

n = 106 patients
Med FU = 28 months

Dupuis J et al, J Clin Oncol 2012
Quantitative assessment of postinduction PET (ΔSUVmax 67%)

PFS according to PET0-8 reduction of average SUV (67.4 threshold)

With Number of Subjects at Risk and 95% Confidence Limits

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET0-8 reduction of Median max SUV &lt;=67.4%</td>
<td>20</td>
<td>55% (11)</td>
<td>45% (9)</td>
</tr>
<tr>
<td>PET0-8 reduction of Median max SUV &gt;67.4%</td>
<td>60</td>
<td>16.8% (15)</td>
<td>81.3% (55)</td>
</tr>
</tbody>
</table>

Reference is at SUV reduction >=43.3%

2y PFS 85%
2y PFS 44%

OS according to PET0-8 reduction of average SUV (67.4 threshold)

With Number of Subjects at Risk and 95% Confidence Limits

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<td>PET0-8 reduction of Median max SUV &lt;=67.4%</td>
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<td>20% (4)</td>
<td>80% (15)</td>
</tr>
<tr>
<td>PET0-8 reduction of Median max SUV &gt;67.4%</td>
<td>60</td>
<td>1.3% (1)</td>
<td>98.8% (75)</td>
</tr>
</tbody>
</table>

Reference is at SUV reduction >=43.3%

2y OS 100%
2y OS 87%
Total metabolic tumour volume and Total Lesion Glycolysis

- **TMTV**
  - Computed using the $\text{SUV}_{\text{max}}$ 41\% threshold
  - Sum of the local metabolic volumes

- **TLG**
  - Sum of local metabolic volumes times their local $\text{SUV}_{\text{max}}$

Meignan, EJNMMI, 2014
Baseline TMTV prognostic value

n = 81 (fused PET-CT images)

TMTV
- mean = 462
- median = 303
- range 1-2401
- AUC 0.63 Cut-off TMTV >938 cm$^3$
  - 12/81 (15%)

Of the 12 patients:
- 9 had stage IV disease
- 9 in int-high FLIPI group
- more nodal sites
- bulk >7 cm % similar in both groups

Population with SUV$_\text{max}$ >13.7
- n=21
- all had MTV <938 cm$^3$
On planned multivariate analysis…

In 81 patients with only 28mo follow-up, on

univariate analysis of TMTV & GELF factors, and
univariate analysis of TMTV & FLIPI factors,

only TMTV was a significant predictor of PFS: HR 4.
Baseline TLG prognostic value

- TLG
  - mean = 2022
  - median = 1464
  - range 4-9396
  - AUC only 0.56 for best cut-off TLG >2912

- 2y PFS: 83% (Population with SUV_{max}>13.7)
  - HR = 2.6

- Population with SUV_{max}>13.7
  - n=21
  - 5/19 had TLG >2912
should we persevere in examining TMTV in Follicular Lymphoma?
The new “gold standard” vs. TMTV

**Post-induction:**
5PS Cut-off ≥4

**Pre-induction:**
TMTV
Yes, we should persevere!!

... in larger populations (both symptomatic and asymptomatic)
... with longer follow-up
... with differing therapies

Potential for exploratory studies within existing large scale trials (already with years of follow-up) using Bendamustine, Obinutuzumab, lenalidomide: ...

BRIGHT, GALLIUM, RELEVANCE, FOLL12

... so before we all retire we may obtain robust OS data based on pre-treatment PET to better identify the small but significant population for whom follicular lymphoma is not an indolent disease.