The role of PET-CT in Follicular Lymphoma
“Prognostic and Predictive”

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Massimo Federico – University Modena
Menton 2012
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
7. Incurable disease
The changing face of FL in recent years

1. Common B-cell lymphoma - >60yrs is not so old!
2. Better 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 or salvage therapies
5. Risk of transformation into aggressive NHL
6. Death from lymphoma becoming a later event
7. Potentially curable disease
Follicular lymphoma: Prognosis: Pre-treatment

Histology
• Grade 1-3a correlates poorly with outcome
• Poor reproducibility 3a vs. 3b
• Transformation to Gd3b poor risk - requiring anthracyclines

Recognised heterogeneity in patient outcomes
• FLIPI (>4 Nodal areas / LDH / Age>60 / Stage III-IV / Hb<12) Solal-Celigny 2004
  – 5yr OS 91 vs. 53%, Low vs. High risk
  – 10yr OS 71 vs. 36%
• FLIPI2 (B_2M>ULN / LoDLIN>6cm / BMI / Hb<12 / Age>60) Federico 2009
  – 3yr PFS 89 vs. 57%
  – 3yr OS 99 vs. 82%
Treatment of symptomatic Stage II-IV Follicular Lymphoma

Practice advances improving PFS: (& probably OS with longer f/u)

• Chemotherapy backbone
  - CHOP supplanting CVP (& Fludarabine) with better PFS (PRIMA and FOLL05)
  - Bendamustine supplanting CHOP with better PFS (STiL)

• Addition of Rituximab
  - to induction chemotherapy
  - as maintenance therapy (EORTC and PRIMA)

Difficult to predict median OS of newly diagnosed patient in 2012
• >10-15 years? i.e. an effective cure for many
PET at **Diagnosis** in FL

- Almost universally but not uniformly FDG avid
- PET at diagnosis does not always equal pre-treatment PET
- $\text{SUV}_{\text{max}} \geq 10$ correlates with treatment within 6/12 (n=78)
  - Svoboda ASH 2011
- Potential relevance for Watch and Wait approach / timing of clinical + imaging follow-up
PET Staging of FL

- To identify localised disease (~10%) amenable to RT
- PET upstaging:
  - 18-31% overall  
  - early stage up to 60%  
    Luminari ASH 2011
- More extranodal disease: ~50% bone, spleen, GIT, skin  
  Tychyj-Pinel ICML 2011, Luminari ASH 2011
- Limited sensitivity/specificity for BM involvement
  - In patients with BMI only 34% were PET+
  - In PET-ve 43% of patients had BMI  
    Luminari ASH 2011
Pre-treatment SUV in FL

- Earlier small studies, patient and scan heterogeneity
- Poor correlation of $SUV_{\text{max}}$ with histologic grade
  - Wohrer 2006, Karam 2006
- No clear cut-off defines transformation
  - $SUV_{\text{max}} < 11.7$ = indolent disease, $SUV_{\text{max}} > 17$ always = transformation
  - Bodet-Milin 2008
- Biopsy the most FDG avid lesion to detect transformation?
  - Often logistically difficult in abdomen. Relevant if using R-CHOP?
- Proposed that intra-patient range in $SUV_{\text{max}}$ i.e. highest – lowest more discriminatory for transformation than $SUV_{\text{max}}$?
  - Wondergem ASH 2011
3 multicentre first-line studies in AS FL

- PET in PRIMA  \textit{Trotman / Salles}
- FOLL05  \textit{Luminari / Federico}
- PET Folliculaire  \textit{Dupuis / Meignan}

- Each with limitations
- Each with the same messages
- >350 patients in total
PRIMA PET Analysis  Trotman J, JCO 2011

- 120 scans at diagnosis, 122 post-induction
- Positive or negative scan defined by local investigator
- Post-induction scan within 3 months of last chemo
FOLL05 Study

Federico M, ASH 2011

FOLLICULAR NHL
Grade I-II-IIIa
Age 18-75
Stage II-IV
Active disease

*RANDOM

Arm 1
R-CVP
every 21 days

Arm 2
R-CHOP
every 21 days

Arm 3
R-FM
every 21 days

≥ PR

≥ PR

≥ PR

FOLL05 Study

504 patients:
122 baseline PET
114 postinduction PET

every 21 days

+ 2 Rituximab every 21 days

+ 2 Rituximab every 21 days

+ 2 Rituximab every 21 days
PET Foliiculaire

PET n°1
n = 118

PET n°2
n= 111

PET n°3
n=106

R-CHOP x 6  +  R x 2

FOLLOW-UP

Dupuis J 2012
<table>
<thead>
<tr>
<th></th>
<th>PRIMA Trotman, JCO 2011</th>
<th>PRIMA Central review. Tychyj-Pinel, ICML 2011</th>
<th>FOLL05 Luminari, ASH 2011</th>
<th>PET Folliculaire Dupuis, Menton in press JCO 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>120</td>
<td>59</td>
<td>122</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td></td>
<td>Retrospective</td>
<td>Prospective</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>R-CHOP (75%), R-CVP +/- R maintenance</td>
<td></td>
<td>R-CHOP vs. R-CVP vs. R-FM</td>
<td>R-CHOP</td>
</tr>
<tr>
<td><strong>% PET+ at diagnosis</strong></td>
<td>99</td>
<td>98</td>
<td>98</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18% upstaged</td>
<td></td>
</tr>
<tr>
<td><strong>SUV_{max} range</strong></td>
<td>na</td>
<td>4.6-35.0</td>
<td>na</td>
<td>3.3-35.6</td>
</tr>
<tr>
<td><strong>SUV_{max} median</strong></td>
<td>na</td>
<td>10.7 Higher in mediastinum &amp; abdomen than peripheral nodes</td>
<td>na</td>
<td>9.5</td>
</tr>
<tr>
<td><strong>Extranodal</strong></td>
<td>na</td>
<td>52% Bone/spleen/GIT/skin</td>
<td>46% Bone/spleen/GIT</td>
<td>na</td>
</tr>
</tbody>
</table>
In this dense slide I suggest to report list of sites, like PRIMA column; then Bone, Spleen, GIT FOR BONE, PET and Histo agreement was 60%. This was mostly represented by agreement on negative cases 44%. Cases with boths histo and PET positive were 24/142 (17%)
Pre-treatment SUV in FL

PET Folliculaire  Dupuis, Menton 2012

\[ \text{SUV}_{\text{max}} > 14 \ (75^{\text{th}}\%) \]
Pre-treatment FLIPI and SUV

PET Folliculaire  Dupuis, Menton 2012

$\text{SUV}_{\text{max}} > 14$ and FLIPI $3-5$
Post-induction therapy:
Limitations of conventional response assessment:

**CT:**
- Limited capacity to assess extranodal disease
- No prognostic impact of CR/CRu/PR in all 3 studies at 24-42m f/u
- Took 10 years to demonstrate an OS impact of CR/CRu over PR

**Molecular remission**
- Restricted primer sets and sensitivity issues
- No universal marker (unavailable in~50%)
- Bcl2 discordance in marrow, blood and nodal compartments
- Timing of MRD is uncertain
- BMBx not appealing to patients!

Bachy 2009
IHP Revised response criteria:
“PET not routinely recommended pre-treatment or for response assessment in FL”
Cheson 2007

• Has the heterogeneity of uptake and indolent/incurable nature of FL fostered scepticism of the role of PET and a paucity of studies?

• Yet widespread clinical PET use internationally

• Not reimbursed for FL in Germany, Australia. Elsewhere?
# Post-induction PET-CT

<table>
<thead>
<tr>
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<th>PRIMA Central review</th>
<th>FOLL05</th>
<th>PET Folliculaire</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PET+ after induction</strong></td>
<td>32/122, 26%</td>
<td>IHP 2007, 22% 5PS ≥3, 22% 5PS ≥4, 13%</td>
<td>26/104*, 25%</td>
<td>23/106, 22% 5PS ≥4</td>
</tr>
<tr>
<td><strong>PET assessment</strong></td>
<td>Local clinician interpretation of PET report</td>
<td>Central review x2 + adjudicator κ 0.83/0.84/0.91</td>
<td>Local interpretation Few centrally reviewed</td>
<td>Central review x3 κ 0.7</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>33 vs. 71% at 42mo</td>
<td>25 vs. 61% at 42mo</td>
<td>48 vs. 84% UVA at 36 mo</td>
<td>51 vs. 87% at 24 mo</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>21mo vs. NR&gt;52mo</td>
<td>HR 3.0, p=0.01</td>
<td>HR 2.3, p=0.036</td>
<td>HR 6.6, p&lt;0.0001</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>79 vs. 97% 42mo</td>
<td>NS, p=0.26</td>
<td>NS, p=0.26</td>
<td>2yr 88 vs. 100%</td>
</tr>
</tbody>
</table>

**Note:** The table includes the proportion of patients with positive (PET+) and negative (PET-) results after induction therapy, along with the central review interpretation and adjudication agreements. The table also presents the progression-free survival (PFS) and overall survival (OS) data, with hazard ratios (HR) and p-values for comparison.
PFS

PRIMA
(med 42mo f/u)

FOLL05
(med 28mo f/u)

PET Folliculaire
(med 24mo f/u)
Technical issues

Reporter concordance
• PET Folliculaire: 3 reviewers κ 0.7
• PRIMA central review: 2 reviewers κ 0.8-0.9
• Better with standardised acquisition and modern scanners?

Metabolic tumour volume? Total Lesion Glycolysis?

Role of contrast enhanced PET/CT?

What criteria for post-induction PET+?
• 5PS (cut off ≥4)? Lower cut-off in relapsed setting?
• What about residual uptake in large mesenteric masses?
  Role for comparison of pre- and post treatment PET / ΔSUVmax?
ΔSUV in FL

PET Folliculaire  Dupuis, Menton 2012

ΔSUV<sub>max</sub> < 67%
Interim PET

- PET Folliculaire study – iPET+ after 4 R-CHOP
- 2yr PFS 61% vs. 86% in PET+ (p=0.0046)
- Lower PPV than postinduction
- ΔSUV after 4 cycles predictive for PFS

- Very good NPV in both PRIMA and PET Folliculaire studies
- Not the same clinical urgency to detect the poor risk population as in HL and DLBCL
PET after 2\textsuperscript{nd} line therapy
Ysebaert, ASH 2011

- 41 patients treated with either R-FC/R-DHAP + ASCT
- CR/CRu in 68/72%
- PET negative 24/36%
- Achieving PET negative status after re-induction the only factor associated with superior OS post-autograft (p=0.0003)
Summary:
PET in FL at Diagnosis/Pre-Treatment

- Universally, but not uniformly, FDG avid lymphoma
- Upstaging in ~20%, higher in Early Stage
- ~50% patients have extranodal involvement
- Poor sensitivity for BM involvement
- Role of SUVmax in predicting time to treatment during W & W?
- Role of SUVmax in predicting treatment outcome?
- Role of SUVmax in directing biopsy to identify transformation?
Summary: Post-induction PET status

• Highly prognostic for both PFS and OS after first line R-CHOP
  Identifies ~25% patients for whom FL is not an indolent disease
• Time to incorporate PET in international response criteria
• Response adapted therapies require study
• 5PS cut-off ≥4 a promising platform. $\Delta$SUV$_{\text{max}}$?

Caveats:
• Insufficient data in context of Rituximab maintenance
• No data on patients receiving Rituximab - Bendamustine
  (GALLIUM study: PET pre-treatment and post-induction in >170 FL patients with ~70% receiving Bendamustine chemotherapy in Ga101 vs. Rituximab RCT)
• No data for Rituximab - Lenalidomide (RELEVANCE study)
What does the clinician /patient want in a post-treatment prognostic factor?

- **Good PPV**
  Important for study of a response directed intensification of therapy
- **Good NPV**
  Reassurance
- **Better sensitivity?**
  Probably not – we know FL remains ‘incurable’.
  We want to detect active disease most likely to progress early.
- **Better specificity?**
  No. The experienced PET physician can distinguish FL from other pathologies, but ... specificity surely better with comparison of pre & post therapy scans cf. isolated interpretation according to 5PS?
PET in Follicular Lymphoma:
Lessons learnt from other lymphomas
What should the next FL studies be?

What we need?

Larger cohorts to better characterise pre-treatment PET

- correlation with histologic grade?
- impact of SUVmax on both Time, and Response, to First Treatment?
- impact on the role of W and W and Rituximab monotherapy?
What should the next FL studies be?

Questions

• Can we now derive a Post-induction FLIPI?

• Can a post-treatment PET adapted therapeutic approach improve outcomes in patients remaining PET+?
  
  What therapy to study: ASCT? RIT? Lenalidomide? other?

• Given the current crowded first-line FL study arena and the principle of therapy intensification is a response adapted approach best studied first in relapse?
  
  Australian study 2013 – Lenalidomide consolidation in relapsed FL remaining PET+ after R-chemo. 1° endpoint: conversion of PET+ to PET-
Impact of final PET result on PFS, in absence of maintenance

Follow-up: 28 months

Final PET+: 24%

3yr PFS:
- 37% PET+
- 69% PET-

Cox regression for PFS:
- PET+ (HR 3.8; IC 2.1 - 6.7)
- FLI2 3-5 (HR 2.5; IC 1.5 - 4.2)
- F gender (HR 0.4; IC 0.3 - 0.8)
- <CR (HR 1.4; IC 0.8 - 2.3)
Conclusion from these studies

In FL patients treated in first line, FDG-PET performed either after 4 cycles of R-CHOP or at the end of immunochemotherapy is strongly predictive of outcome.

FDG-PET in Follicular Lymphoma?

Therapeutic intervention based on PET results after induction treatment should be evaluated in the future.
A multicenter, phase III, randomized study to evaluate the efficacy of a response-adapted strategy to define maintenance after standard chemoimmunotherapy in patients with advanced-stage Follicular Lymphoma
OBJECTIVES

Primary objective

To evaluate whether a PET and MRD response-based maintenance therapy is more effective in terms of Progression-Free Survival (PFS) than a standard maintenance therapy with Rituximab in patients with untreated, advanced, follicular lymphoma.
Secondary objectives

• To evaluate the efficacy of maintenance with observation or pre-emptive Rituximab therapy administered on the basis of MRD status in patients at low risk of progression after induction chemoimmunotherapy.

• To evaluate the efficacy of intensified maintenance with (90)Y Ibritumomab Tiuxetan followed by Rituximab maintenance therapy in patients at high risk of progression after induction chemoimmunotherapy.

• To compare a response-based maintenance therapy with a standard maintenance therapy in terms of toxicity.
TRIAL DESIGN

Induction therapy

Randomization

Standard arm

Experimental arm

Salvage

<PR

4 x R-CHOP

2x R-CHOP + 2R

PET

MRD

LF st II-IV
Age >18
Active disease
FLIPI2>O

4 x R-CHOP
Central review:
Five expert nuclear medicine reviewers will score the scans according to the Deauville score.
**TRIAL DESIGN**

**Maintenance**

- **CR, PR**
  - **R Maintenance every 2 months x 2yrs**
  - **<PR**
  - **Salvage**

**Standard arm**

**Experimental arm**

**Induction therapy**

**Patients with no molecular markers**

- **PET-**
  - **MRD**
  - **Neg**
    - **Observation**
  - **Pos**
    - **Rituximab weekly x 4**

- **PET+**
  - **(90)Y Ibritumomab Tiuxetan + R Maintenance every 2 months x 2yrs**
  - **<PR**
  - **Salvage**
Inclusion criteria(1)

• Histological diagnosis of B-Cell Follicular Lymphoma (FL), grade I, II, IIIa according to WHO classification

• ECOG performance status 0-2

• Age ≥18 years

• Ann Arbor stage II-IV

• FLIPI2 score > 0

• Presence of evaluable/measurable disease after diagnostic biopsy
Inclusion criteria(2)

• At least one of the following criteria for defining active disease:
  - systemic symptoms
  - cytopenia due to bone marrow involvement
  - LDH> upper normal value
  - any nodal or extranodal tumor mass with a diameter >7cm
  - involvement of >= 3 nodal sites, each with a diameter of >= 3cm
  - extranodal disease
  - rapidly progressive disease
FOLL12 sample size and activation status

**Accrual**  4 years
**Follow-up**  3 years from the last accrued

Sample Size  $546 + 10\% \text{ dropout}^* = 602 \ (301 \text{ by arm})$

70-75 participating sites

First active site: **Messina Papardo**  
*(EC approval 25/07/2012)*
What should the next FL studies be?
What we need?
Larger cohorts

YES
What should the next FL studies be?

Can we now derive a Post-induction FLIPI?

We will check!!
What should the next FL studies be?

Can a post-treatment PET adapted therapeutic approach improve outcomes in patients remaining PET+?

FOLL12 has been designed with this ambitious goal!
What should the next FL studies be?

Given the first-line FL study arena and the principle of therapy intensification, should a response adapted approach be investigated in patients with relapsed FL?

YES, a response adapted approach should be also investigated in patients with relapsed FL.
RESPONSE ADAPTED THERAPY

NEW DRUGS

... ¿will allow us ...?

Picasso - Muerte del toro
Remission monitoring

• No data
• No reason to think it would be worthwhile given poor specificity in other lymphoma histologies
• No rationale given re-treatment is usually reserved until symptomatic progression/relapse