How I approach newly diagnosed Follicular Lymphoma patients with advanced stage?

Professeur Gilles SALLES
How I Choose First Line Treatment in Follicular Lymphoma in 2017?

1. How do I take into account the heterogeneity of patients with advanced stage FL?

2. Choosing first line therapy: standards or options?

3. What is next in first line therapy?
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The Follicular Lymphoma International Prognostic Index (FLIPI): Overall survival


- Age < 60 vs. ≥ 60
- Hemoglobin level ≥ 12g/dL vs. < 12g/dL
- Serum LDH level ≤ ULN vs. > ULN
- Ann Arbor stage I – II vs. III – IV
- Number of nodal sites involved ≤ 4 vs. > 4
Improving FLIPI: may be FLIPI-2?


59% of patients had received rituximab; assess both PFS and OS

### Risk groups

- **Good**
  - Age ≤ 60 vs. > 60
  - Hemoglobin level ≥ 12g/dL vs. < 12g/dL
  - β2 microglobulin ≤ ULN vs. > ULN
  - Bone marrow involvement no vs. yes
  - Largest diameter of the largest node ≤ 6 cm vs. > 6 cm

- **Intermediate**
  - 1 – 2 factors
  - Age < 60 vs. > 60
  - Hemoglobin level ≥ 12g/dL vs. < 12g/dL
  - β2 microglobulin ≤ ULN vs. > ULN
  - Bone marrow involvement no vs. yes
  - Largest diameter of the largest node ≤ 6 cm vs. > 6 cm

- **Poor**
  - ≥ 3 factors
  - Age < 60 vs. > 60
  - Hemoglobin level ≥ 12g/dL vs. < 12g/dL
  - β2 microglobulin ≤ ULN vs. > ULN
  - Bone marrow involvement no vs. yes
  - Largest diameter of the largest node ≤ 6 cm vs. > 6 cm

### Graphs

- **PFS**
  - Log-rank 64.6 \( P < .0001 \)
- **OS**
  - Log-rank 49.9 \( P < .0001 \)

59% of patients had received rituximab; assess both PFS and OS.
Despite progress in understanding FL biology, clinical features still guide treatment decision

- Ann Arbor stage, symptoms, LDH and b2microglobulin
- FLIPI and FLIPI2 indexes
- Tumor burden criteria

**GELA criteria**

- High tumor bulk defined by either:
  - a tumor > 7 cm
  - 3 nodes in 3 distinct areas each > 3 cm
  - symptomatic splenic enlargement
  - organ compression
  - ascites or pleural effusion
- Presence of systemic symptoms
- Serum LDH or β2-microglobulin above normal values

**BNLI criteria**

- Rapid disease progression in the preceding 3 months
- Life threatening organ involvement
- Renal or liver infiltration
- Bone lesions
- Systemic symptoms or pruritus
- Hb<10 g/dL or WBC< 3.0×10^9/L or Plat.<100×10^9/L ; related to marrow involvement
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Choosing first line therapy in patients with advanced stage: standards or options

1. Rituximab plus chemotherapy represents the standard of care

2. Is there an optimal chemotherapy regimen?
   - R-CVP, R-CHOP, R-FC/FM/FCM or R-Benda.

3. What is the benefit of further consolidation?
   - radioimmunotherapy, rituximab maintenance
High tumor burden follicular lymphoma (FL2000 update)

Event free survival

Overall survival

8-year EFS=44%

8-year OS=79%

median follow-up = 8.3 years

Bachy et al, Haematologica 2013
Rituximab + chemotherapy has improved overall survival

<table>
<thead>
<tr>
<th>Study name and author</th>
<th>Follow-up</th>
<th>Overall survival (%)</th>
<th></th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>M3902; Marcus et al.(^1)</td>
<td>4 years</td>
<td>77</td>
<td>83</td>
<td>✓</td>
</tr>
<tr>
<td>GLSG; Hiddemann et al.(^2)</td>
<td>5 years</td>
<td>84</td>
<td>90</td>
<td>✓</td>
</tr>
<tr>
<td>M39023; Herold et al.(^3)</td>
<td>4 years</td>
<td>75</td>
<td>89</td>
<td>✓</td>
</tr>
<tr>
<td>FL2000; Salles et al.(^4)</td>
<td>8 years</td>
<td>79</td>
<td>84</td>
<td>(high risk pts)</td>
</tr>
</tbody>
</table>

Cochrane analysis:
HR = 0.63 [0.51–0.79]

Randomized trial comparing rituximab-CHOP versus CHOP followed by $^{131}$I tositumomab (CHOP-RIT) in untreated follicular lymphoma (SWOG S0016)

Progression free survival

Overall survival

Significantly more Gr. 3 or more febrile neutropenia with R-CHOP, and more Gr. 3 thrombocytopenia with CHOP+RIT

AML/MDS: 3 cases of with R-CHOP and 8 cases in CHOP-RIT (non significant)

Press O et al, JCO January 20, 2013 vol. 31 no. 3 314-32
Progression-Free Survival

Median Follow-up: 9.6 Years

CHOP + I-131

CHOP + R

At Risk
CHOP + I-131 264
CHOP + Rituximab 267
Failed
CHOP + I-131 113
CHOP + Rituximab 146
10-year Estimate
CHOP + I-131 57%
CHOP + Rituximab 42%

P = .01

Year After Randomization

0 5 10 15
All chemo regimen are not equal:
PRIMA study:
PFS from registration by induction regimen

Morschhauser et al., ICML 2011
All chemo regimen are not equal:
PRIMA study:
OS from registration by induction regimen

R-CHOP 93.2% (91.2–94.7%)
R-CVP 88.3% (83.4–91.9%)
R-FCM 74.1% (57.9–84.8%)

Morschhauser et al., ICML 2011
Italian FIL foll05 study: PFS by arm (N=504)

Federico M et al. J Clin Oncol. 2013 Apr 20;31(12):1506-1
R-Bendamustine versus R-CHOP

Progression free survival follicular lymphoma (n=279 pts)

Lower toxicity of B-R

Median (months)
- B-R: n.y.r.
- CHOP-R: 40.9

Hazard ratio, 0.61 (95% CI 0.42 - 0.87)
p = 0.0072

Rummel et al, Lancet 2013
R-Bendamustine versus R-CHOP
Progression free survival follicular lymphoma (n=279 pts)

Some questions:
- Only grade 1-2 FL in the trial
- Poor results of the R-CHOP arm?
- Early results reported at ASH 2007?
- Long term toxicity of benda??
- Lack of OS benefit

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p = 0.0072

Will be updated at ASCO 2017...
90Y Ibritumomab tiutexan (RIT) consolidation in FL patients after chemotherapy (FIT trial)
Progression free survival in all patients

- Very high complete response rates after RIT
- But few patients had received Rituximab - chemo as induction
- Secondary malignancies 26 after RIT vs. 14 without (including 7 vs. 1 MDS/AML)

Morchhauser et al, J Clin Oncol, 2013 Apr 1. [Epub ahead of print]
In patients responding to R-CHOP, is radio-immunotherapy better than rituximab maintenance?

Lopez Guillermo et Al, ASH 2013, abstract 369
PRIMA: study design

**INDUCTION**

- High tumor burden
- Untreated follicular lymphoma
- Registration

- Immunochemotherapy
  - 8 x Rituximab
  - +
  - 8 x CVP or
  - 6 x CHOP or
  - 6 x FCM

**MAINTENANCE**

- Rituximab maintenance
  - 375 mg/m²
  - every 8 weeks
  - for 2 years‡

- Observation‡

- Random 1:1*

- CR/CRu PR

- PD/SD off study

* Stratified by response after induction, regimen of chemo, and geographic region

‡ Frequency of clinical, biological and CT-scan assessments identical in both arms

Five additional years of follow-up
PRIMA 6 years follow-up
Progression free survival from randomization

Median follow-up since randomization: 73 months
PRIMA 6 years follow-up
Progression free survival from randomization

R-CHOP induction

PFS according to maintenance arm stratified on induction (ITT patients) (R-CHOP)

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95%CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBSERVATION</td>
<td>386</td>
<td>56.2% (217)</td>
<td>43.8% (169)</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>382</td>
<td>38.5% (140)</td>
<td>63.4% (242)</td>
</tr>
</tbody>
</table>

HR = 0.538, P < .0001

R-CVP induction

PFS according to maintenance arm stratified on induction (ITT patients) (R-CVP)

<table>
<thead>
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<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95%CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBSERVATION</td>
<td>113</td>
<td>59.3% (67)</td>
<td>48.7% (45)</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>109</td>
<td>48.6% (53)</td>
<td>51.4% (55)</td>
</tr>
</tbody>
</table>

HR = 0.697, P = .05

Median follow-up since randomization: 73 months
PRIMA 6 years follow-up
Overall survival

Median follow-up since randomization: 73 months

OS according to maintenance (ITT patients)
With Number of Subjects at Risk and 95% Confidence Limits

6 years = 88.7%
6 years = 87.4%

HR = 1.027
P = .885

<table>
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<tr>
<th></th>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95%CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBSERVATION</td>
<td>513</td>
<td>11.3% (58)</td>
<td>88.7% (455)</td>
<td>NA (NA; NA)</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>505</td>
<td>11.7% (59)</td>
<td>88.3% (446)</td>
<td>NA (NA; NA)</td>
</tr>
</tbody>
</table>
My choices in high tumor burden patients

1. Most cases
   - R-CHOP followed by R maintenance

2. If contra-indication to anthracycline
   - B-R +/- maintenance
   - Rituximab single agent?
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GALLIUM: Obinutuzumab in 1st line ttt R-chemo versus G-chemo - IRC-assessed PFS (FL)

Marcus RE et al, ASH 2016, Abstract 6

R-chemo, n=601  G-chemo, n=601

<table>
<thead>
<tr>
<th>Pts with event, n (%)</th>
<th>125 (20.8)</th>
<th>93 (15.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr PFS, % (95% CI)</td>
<td>77.9 (73.8, 81.4)</td>
<td>81.9 (77.9, 85.2)</td>
</tr>
<tr>
<td>HR (95% CI), p-value*</td>
<td>0.71 (0.54, 0.93), p=0.0138</td>
<td></td>
</tr>
</tbody>
</table>

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

No. of patients at risk
R-chemo  601 563 500 460 372 263 160 66 10 0
G-chemo  601 569 528 491 385 270 162 73 10 0

Marcus RE et al, ASH 2016, Abstract 6
**GALLIUM: toxicities according to treatment arms**

**Grade 5 (fatal) AEs by treatment (FL)**

*Includes only pts who died before clinical cut-off date; †this patient (G-B group) was initially assigned three causes of death (Clostridium difficile colitis, prostate cancer, and myelodysplastic syndrome); Clostridium difficile colitis was the most acute, so the patient has been assigned to the ‘Infections and infestations’ category and the number of fatal AEs in G-B pts in neoplasms SOC reduced from 5 to 3*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>Infectious</th>
<th>Induction</th>
<th>Maintenance</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>GB</td>
<td>N=337</td>
<td>19 (5.6%)</td>
<td>9 (2.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RB</td>
<td>N=338</td>
<td>15 (4.4%)</td>
<td>2 (0.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G-ChOP</td>
<td>N=191</td>
<td>3 (1.6%)</td>
<td>1 (0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-ChOP</td>
<td>N=201</td>
<td>4 (2.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G-CVP</td>
<td>N=61</td>
<td>1 (1.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-CVP</td>
<td>N=56</td>
<td>1 (1.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prognostic Value of PET-CT After Frontline Therapy in FL

Total Metabolic Tumor Volum (TMTV) at diagnosis accurately predicts outcome

Meignan et al., JCO 2016
(A) Overall survival (OS) from a risk-defining event after diagnosis in patients who received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in the National LymphoCare Study group.

No. at risk
Early POD 110  82  66  56  59  42  32  14  3
Reference 420  408  387  363  344  253  145  34  0

Carla Casulo et al. JCO 2015;33:2516-2522

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Improving clinical indexes with mutations or GEP?

m7-FLIPI

POD24-PI

23-gene score


Huet et al. Submitted

Median 10.8 y

Median 3.1 y
The increase in patients survival implies new challenges

Important endpoints for future/ongoing studies evaluating therapeutic strategies in FL:

- Quality of response
- Surrogate for PFS?
- Quality of life
- Ability to deliver second line treatments
- Long term toxicities

... and Overall Survival