OPEN QUESTIONS IN THE TREATMENT OF FOLLICULAR LYMPHOMA

Michele Ghielmini
Oncology Institute of Southern Switzerland
Bellinzona
10 QUESTIONS

1. Is follicular lymphoma (FL) still incurable?
2. How should early stage be managed?
3. Is Watch and Wait still acceptable?
4. Which chemotherapy is the best?
5. Should everybody receive R-maintenance?
6. What is the role of chemo-free options?
7. How to treat high-risk cases?
8. Should Grade 3 FL be treated differently?
9. Which are the indications for transplantation?
10. How to manage transformation to DLBCL?
THE MEDIAN OS RAISED FROM 10 TO 18 Y BUT ADVANCED FL REMAINS UNCURABLE

Stanford\(^1\), n = 1334

\[\text{Median OS:}
\begin{align*}
\text{Era 1:} & \quad 11.0 \text{ yrs} \\
\text{Era 2:} & \quad 11.0 \text{ yrs} \\
\text{Era 3:} & \quad 18.5 \text{ yrs} \\
\text{Era 4:} & \quad \text{Not reached} \\
\text{Overall:} & \quad 13.6 \text{ yrs}
\end{align*}\]

P < 0.001

Swedish registry\(^2\), n = 2641

1. Republished with permission of the American Society of Hematology from Blood, Tan D, et al. 122(6), 2013; permission conveyed through Copyright Clearance Center, Inc.;
90% OF FL AGED <40 ARE ALIVE AT 10 YEARS
The median survival of FL patients aged <40 is expected to be >30 years!

N=155/1002; 4 EU centres\(^1\)
(Bellinzona, Novara, Barcelona, London)

N=164/2652; Lymphocare\(^2\)

FL PATIENTS RELAPSING WITHIN 24 MONTHS

FL patients relapsing within 24 months from the end of immunochemotherapy (POD24) have a worse outcome.


2. Republished with permission of the American Society of Hematology from Blood, Jurinovic V, et al. 128(8), 2016; permission conveyed through Copyright Clearance Center, Inc.
FL IS CURABLE IN SOME CASES!

- Early stage
  - 50% cured with RT

- Grade 3B
  - 50% cured with R-CHOP

- Allogeneic transplantation
  - 50% cured with GvHD
10 QUESTIONS

1. Is FL still incurable?
2. How should early stage be managed?
3. Is Watch and Wait still acceptable?
4. Which chemotherapy is the best?
5. Should everybody receive R-maintenance?
6. What is the role of chemo-free options?
7. How to treat high-risk cases?
8. Should grade 3 FL be treated differently?
9. Which are the indications for transplantation?
10. How to manage transformation to DLBCL?
40–60% OF EARLY STAGE FL IS CURED BY EXCLUSIVE RT

Relapse after RT: The Princess Margaret Cancer Centre* experience

* The Princess Margaret Cancer Centre, Toronto, Canada.
310 ST I-II FL STAGED BY PET AND TREATED WITH RT ONLY

Retrospective study from 11 centres in 3 continents

FFP at 5 years
Stage I  = 74.3%
Stage II = 48.1%

FFP by stage

Freedom from progression (percent)

At risk
Stage I  410  305  165  84  34  20  5
Stage II  102  61  34  19  12  8  1

Republished with permission of the American Society of Hematology from Blood, Brady JL, et al. 133(3), 2019; permission conveyed through Copyright Clearance Center, Inc.
PROSPECTIVE RANDOMISED STUDY IN STAGE I–II FL RT +/- (R)-CVP

N=150

HR 0.62; p=0.40

p=0.045
EFFECT OF RITUXIMAB ADDED TO RT IN EARLY STAGE (I, II) FL

Previously untreated FL
Stage I–II, G1–3°

Cohort 1
n=51
RT only

Cohort 2
n=43
Rx4 >RT

10-year PFS: 51%
10-year OS: 84%

10-year PFS: 65%
10-year OS: 94%

10 QUESTIONS

1. Is FL still incurable?
2. How should early stage be managed?
3. Is Watch and Wait still acceptable?
4. Which chemotherapy is the best?
5. Should everybody receive R-maintenance?
6. What is the role of chemo-free options?
7. How to treat high-risk cases?
8. Should grade 3 FL be treated differently?
9. Which are the indications for transplantation?
10. How to manage transformation to DLBCL?
3 OLD RANDOMISED STUDIES OF W + W VS. IMMEDIATE CHEMOTHERAPY

**W+W vs. ProMACE-MOPP**
89 patients
Young, 1988

**W+W vs. Prednimustine**
130 patients
Brice, 1997

**W+W vs. Chlorambucil**
309 patients
Ardeshna, 2003

HIGH TUMOUR BURDEN VS. SYMPTOMATIC PATIENTS

**GELA criteria**

- High tumour bulk defined by either:
  - a tumour >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-macroglobulin 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 × 10⁹/L or Plat. <100 × 10⁹/L; related to marrow involvement
THE EFFECT OF SINGLE AGENT RITUXIMAB IN ASYMPTOMATIC NON-BULKY FL

UK Intergroup Trial (N=463)

Randomisation

ARM A
Watch and Wait

ARM B
Rituximab Induction

ARM C
Rituximab Induction and maintenance

Clinic visits

Rx4

Continued Follow-up

1 3 5 7 9 11 13 15 17 19 21 23 25 months

RITUXIMAB PROLONGS THE TIME TO NEXT THERAPY, BUT NO EFFECT ON OS

Time to start of new treatment

Overall survival

10 QUESTIONS

1. Is FL still incurable?
2. How should early stage be managed?
3. Is Watch and Wait still acceptable?
4. Which chemotherapy is the best?
5. Should everybody receive R-maintenance?
6. What is the role of chemo-free options?
7. How to treat high-risk cases?
8. Should grade 3 FL be treated differently?
9. Which are the indications for transplantation?
10. How to manage transformation to DLBCL?
THE ONLY IMPROVEMENT IN FL SURVIVAL: THE ADDITION OF RITUXIMAB TO CHEMO

R-CHOP VS. R-FCM VS. R-MCP
GLSG AND OSHO N=205 FL

Hoster E, et al. ICML 2017; Abstract 13. Reproduced with permission from Dr E.Hoster
FOLL05 STUDY: R-CVP VS. R-CHOP VS. R-FC

N=500, median follow-up 7 years

**ITT**

<table>
<thead>
<tr>
<th></th>
<th>HR *(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CVP</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>R-CHOP</td>
<td>0.73 (0.55, 0.98)</td>
<td>0.033</td>
</tr>
<tr>
<td>R-FM</td>
<td>0.70 (0.52, 0.93)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

**TTF**

- R-CVP
- R-CHOP
- R-FM

**OS**

- R-CVP
- R-CHOP
- R-FM

Luminari S, et al. ICML 2017; Abstract 15. Reproduced with permission from Dr S.Luminari
R-BENDA IS AS GOOD (OR BETTER) THAN R-CHOP

FL: StiL vs. BRIGHT study (PFS)

1. Reprinted from The Lancet, 381(9873), Rummel MJ, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial, 1203–10, Copyright 2013, with permission from Elsevier;
10 QUESTIONS

1. Is FL still incurable?
2. How should early stage be managed?
3. Is Watch and Wait still acceptable?
4. Which chemotherapy is the best?
5. Should everybody receive R-maintenance?
6. What is the role of chemo-free options?
7. How to treat high-risk cases?
8. Should grade 3 FL be treated differently?
9. Which are the indications for transplantation?
10. How to manage transformation to DLBCL?
MAINTENANCE MORE THAN DOUBLES PFS, BUT HAS NO EFFECT ON SURVIVAL

The PRIMA trial: 9y median follow up

P<0.0001
HR=0.61 (95%CI) 0.52-0.73

Median: 10.5 y

Log-Rank, P=0.795;
HR=1.04 (95%CI) 0.77-1.40

OS probability

R-maintenance
Observation

10-year OS estimates

GLSG AND OSHO TRIAL
MAINTENANCE QUESTION

median follow-up = 3.2

Obs, median = 4.2
R-maint, median not reached
p = 0.0064

median follow-up = 3.1

Obs, median not reached
R-maint, median not reached
p = 0.95

<table>
<thead>
<tr>
<th>Numbers At Risk</th>
<th>Years from end of induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs</td>
<td>63 55 43 25 11 2 0</td>
</tr>
<tr>
<td>R-maint</td>
<td>65 58 50 36 21 4 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Numbers At Risk</th>
<th>Years from 2nd randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs</td>
<td>64 59 48 30 11 3 1 0</td>
</tr>
<tr>
<td>R-maint</td>
<td>67 60 53 37 19 2 0</td>
</tr>
</tbody>
</table>

Hoster E, et al. ICML 2017; Abstract 13. Reproduced with permission from Dr E.Hoster.
## META-ANALYSIS:
### TOXICITIES OF R-MAINTENANCE

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients, n</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3–4 AE</td>
<td>1598</td>
<td>1.60 (1.29, 1.99)</td>
</tr>
<tr>
<td>AEs with D/C</td>
<td>1433</td>
<td>2.72 (1.30, 5.68)</td>
</tr>
<tr>
<td>Infections</td>
<td>1656</td>
<td>1.67 (1.40, 2.0)</td>
</tr>
<tr>
<td>Grade 3–4 Infections</td>
<td>1656</td>
<td>3.55 (1.88, 6.69)</td>
</tr>
</tbody>
</table>

10 QUESTIONS

1. Is FL still incurable?
2. How should early stage be managed?
3. Is Watch and Wait still acceptable?
4. Which chemotherapy is the best?
5. Should everybody receive R-maintenance?
6. What is the role of chemo-free options?
7. How to treat high-risk cases?
8. Should grade 3 FL be treated differently?
9. Which are the indications for transplantation?
10. How to manage transformation to DLBCL?
SINGLE AGENT RITUXIMAB AS FIRST LINE OBTAINS 70% RR

The duration of response depends on the duration of R-treatment

**EFS**

- Median EFS = 4.4 years
- Median EFS = 2.5 years
- p = 0.045

**PFS**

- Median PFS = 7.4 years
- Median PFS = 3.5 years
- p = 0.04

R2 (RITUXIMAB + LENALIDOMIDE) IS AS ACTIVE AS R-CHEMOTHERAPY

RELEVANCE: Interim PFS and OS

RELEVANCE:
TREATMENT-EMERGENT ADVERSE EVENTS

IDELALISIB IS A PI3K INHIBITOR

126 indolent lymphomas, resistant to alkylating agents and rituximab

ORR 57%

10 QUESTIONS

1. Is FL still incurable?
2. How should early stage be managed?
3. Is Watch and Wait still acceptable?
4. Which chemotherapy is the best?
5. Should everybody receive R-maintenance?
6. What is the role of chemo-free options?
7. How to treat high-risk cases?
8. Should grade 3 FL be treated differently?
9. Which are the indications for transplantation?
10. How to manage transformation to DLBCL?
THE CLINICOGENETIC RISK MODEL M7-FLIPI

**R-CHEMO (CVP) BY FLIPI**

**FLIPI 0-1**
Median EFS: NR

**FLIPI 2**
Median EFS: 40 months

**FLIPI 3-5**
Median EFS: 27 months

311 first-line FL

CVP vs. R-CVP

R gives the smallest benefit in FLIPI high-risk

High-risk worse prognosis despite of R

---

INTENSIFICATION (R-CHOP-14) BY FLIPI

FLIPI 0-1
Median PFS: 5 years

FLIPI 2
Median PFS: 4 years

FLIPI 3-5
Median PFS: 3 years

300 first line FL
R-CHOP21 vs. R-CHOP14
No benefit of intensification for all FLIPI groups
High-risk worse prognosis despite of intensification

HDCT BY FLIPI AT DIAGNOSIS OR AT RELAPSE

18 first-line FL and 34 second-line FL

High-risk FLIPI worse prognosis despite of HDCT

10 QUESTIONS

1. Is FL still incurable?
2. How should early stage be managed?
3. Is Watch and Wait still acceptable?
4. Which chemotherapy is the best?
5. Should everybody receive R-maintenance?
6. What is the role of chemo-free options?
7. How to treat high-risk cases?
8. Should grade 3 FL be treated differently?
9. Which are the indications for transplantation?
10. How to manage transformation to DLBCL?
FL GRADING

LBCL, large B-cell lymphoma
Images courtesy of Dr Stefano A Pileri
Grade 3 FL must be treated with an anthracycline-containing regimen

Follicular lymphoma – mean counts

No adriamycin

Overall survival (%)

Years

p<0.001

Grade 1

Grade 2

Grade 3

Adriamycin

Overall survival (%)

Years

p=0.87

Grade 1

Grade 2

Grade 3


GRADE IS NOT A PROGNOSTIC BUT A PREDICTIVE FACTOR: OMAHA
GRADE 3A VS. 3B IS NOT A PROGNOSTIC BUT A PREDICTIVE FACTOR: NORDIC GROUP

Overall survival

TO BE ON THE SAFE SIDE...

Theoretically: give R-CHOP only to Grade 3B

BUT

30–50% of pathologists do not agree on grade

Practically: R-CHOP to all Grade 3?
10 QUESTIONS

1. Is FL still incurable?
2. How should early stage be managed?
3. Is Watch and Wait still acceptable?
4. Which chemotherapy is the best?
5. Should everybody receive R-maintenance?
6. What is the role of chemo-free options?
7. How to treat high-risk cases?
8. Should grade 3 FL be treated differently?
9. Which are the indications for transplantation?
10. How to manage transformation to DLBCL?
FL: AUTOLOGOUS TRANSPLANT AS FIRST-LINE

GELF: n=402

True also for high FLIPI patients !!

Republished with permission of the American Society of Hematology from Blood, Sebban C, et al. 108(8), 2006; permission conveyed through Copyright Clearance Center, Inc.
HDCT SALVAGE FOR POD24 FL PATIENTS

517 FL patients in Alberta
152 relapsed
84 POD24
68 POD>24

ALLO- SCT FOR RELAPSED FL

1567 registry FL cases
2001–2011
HLA-matched donor

Favourable characteristics
36% had ≥3 previous regimens
29% had previous auto-SCT
76% chemo-sensitive to last TTT
77% non-myeloablative
4 years median time from diagnosis

AUTO- VS. ALLO- SCT FOR POD24 FL

440 POD24 FL receiving transplant
240 Auto
105 MSD
95 MUD

Auto is as active
And safer

10 QUESTIONS

1. Is FL still incurable?
2. How should early stage be managed?
3. Is Watch and Wait still acceptable?
4. Which chemotherapy is the best?
5. Should everybody receive R-maintenance?
6. What is the role of chemo-free options?
7. How to treat high-risk cases?
8. Should grade 3 FL be treated differently?
9. Which are the indications for transplantation?
10. How to manage transformation to DLBCL?
PROGNOSIS OF RELAPSED FL PATIENTS DEPENDS ON TRANSFORMATION (PRIMA TRIAL)

1,018 FL case
463 progressed
194 biopsied
40 histology transformed

OS of relapsed patients in the PRIMA trial

HDCT AT RELAPSE IS USEFUL ONLY IF TRANSFORMED HISTOLOGY

Transformed FL at relapse: ASCT improves survival

FL histology at relapse: ASCT does not influence survival

PROGNOSIS OF TRANSFORMED FL AND R/R DLBCL TREATED WITH SALVAGE CHEMO AND HDCT

From randomisation

429 relapsed DLBCL
87 relapsed transformed FL

Induction: (R) DHAP or (R) GDP
Consolidation: HDCT

Transformed FL have the same outcome as relapsed DLBCL if treated with salvage CT + HDT
ALGORITHM FOR TREATING TRANSFORMED FL

Transformed lymphoma to DLBCL

- No prior chemotherapy (W&W, RT)
  - R-CHOP

- Prior chemotherapy, no (R)-CHOP
  - R-CHOP

- Prior R-CHOP
  - 2nd line CT for DLBCL
    - Young, fit, responding
      - HDT-ASCR
**Prognosis**
- Stage
- FLIPI
- Grade

**Symptoms**
- Not
- Mild
- Life/organ threatening

**Patient priority**
- Longer survival
- Longer remission
- Better quality of life

**Choose among**
- Asymptomatic cases
  - Watch and wait
- Mild symptoms
  - Non-chemo treatment
  - Rituximab single agent
- High tumour burden
  - Chemoimmunotherapy
  - R-bendamustine
  - R-CHOP
  - Consider R-maintenance

**TREATMENT ALGORITHM ESMO 2019 FOR FIRST-LINE FL**
THANK YOU!