Open questions in the treatment of Follicular Lymphoma

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Survival of major lymphoma subtypes at IOSI

NHL outcome, by histology (IOSI database 1979-2006)

CLL/SLL
MCL
FL
MALT
DLBCL
PTCL

Courtesy of Oncology Institute of Southern Switzerland (IOSI)
FL remains an incurable disease, but new therapies have improved survival

MD Anderson

With permission from J Clin Oncol, Liu Qi et al., J Clin Oncol, April 1, 2006, Vol 24 (10):1582-1589

SWOG

Meta-Analysis of Chemo vs. R-Chemo: overall survival

**Study**

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>Weight [%]</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forstpointner 2005</td>
<td>4.76</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Herold 2005</td>
<td>15.13</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Marcus 2005</td>
<td>19.55</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Hiddemann 2005</td>
<td>35.04</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>74.47</strong></td>
<td><strong>0.57 (0.43 - 0.77)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 45/525, 77/490

Heterogeneity: ($P = 0.65$), $I^2 = 0$

Adapted by M. Ghielmini from Schulz H, et al., J Natl Cancer Inst. 2007; 99(9):706-714
Questions in FL

- Is watch and wait still an option?
- Which is the standard first line treatment?
- What is the role of auto/allo-transplantation?
- What is the role of maintenance?
Waiting does not increase the incidence of transformation

BC Cancer Agency, Vancouver

3 randomized studies of W + W vs. immediate chemotherapy

### W+W vs. ProMACE-MOPP
- 89 pts
- Young, 1988

### W+W vs. Prednimustine
- 130 pts
- Brice, 1997

### W+W vs. Chlorambucil
- 309 pts
- Ardeshna, 2003

With permission from The Lancet, Ardeshna K M et al., The Lancet, August 2003, Vol. 362 9383):516-522
Potential advantages of waiting

- Delayed acute side-effects of treatment
- Delayed late side-effects
- Delayed infertility or menopause

Median time to treatment: **3 years**

**25%** of patients still not in need of treatment **at 10 years**

Case 1: 25 year old economist

2001: diagnosis FL IIIa G1, no bulk, FLIPI low risk

WHAT IS YOUR NEXT STEP?

Ghielmini M, Oncology Institute of Southern Switzerland (IOSI)
Case 1: 25 year old economist

- 2001: diagnosis FL IIla G1
- Watch and wait
- LN diameter spontaneously regress with time until CR
- 2011 still in spontaneous CR
Proportion of patients with no new treatment initiated

Time To Initiation of New Therapy (TTINT)

With permission from K.M. Ardeshna; Ardeshna K M et al., ASH 2010, Abstract 6
Questions in FL

- Is watch and wait still an option?

- Which is the standard first line treatment?

- What is the role of auto/allo-transplantation?

- What is the role of maintenance?
RR and OS according to treatment intensity

179 patients/Barcelona (1977-1997)

- Chlorambucil
- CVP
- CHOP

10 years survival
Complete response

With permission from A. López-Guillermo; López-Guillermo A, Leuk Lymph 1994;15:159-65
Prolonged remission does not mean longer survival

Relapse-free survival

\[ P = 0.009 \]

Overall survival

\[ P = 0.107 \]

PFS by subentities for R-bendamustine vs. R-CHOP

Follicular

\[ p = 0.0281 \]

Mantle cell

\[ p = 0.0146 \]

Marginal zone

\[ p = 0.6210 \]

Waldenström

\[ p = 0.0024 \]

EFS according to response to Rituximab Induction Treatment

Event-free survival in randomized follicular lymphoma patients

35% of responders still in remission at 8 years

With permission from J Clin Oncol, Martinelli G et al., J Clin Oncol, Oct 10, 2010: Vol. 28(29); 4480-4484
Case 2: 22 year old cook

- Stage IVa G2 FL, FLIPI interm.
- BM infiltration 30%

WHAT WOULD YOU DO NOW?

Ghielmini M, Oncology Institute of Southern Switzerland (IOSI)
Case 2: 22 year old cook

- 1994: stage IVa G2 FL
- BM infiltration 30%
- Bcl-2 in BM and PB neg
  \[\text{Wait and see}\]
  \[\text{1996 , clear PD}\]
- Chlorambucil for 9 months
  \[\text{Complete remission}\]
- 2004 relapse left tonsil only
  \[\text{Operated}\]
Case 2: 17 years later ...

- is now 39 years old
- has married and
- has two healthy 11 and 7 year old children
- and still so many treatment options for the future ...
Questions in FL

- Is watch and wait still an option?
- Which is the standard first line treatment?
- What is the role of auto/allo-transplantation?
- What is the role of maintenance?
FL: Autologous Transplant in first-line

GELF: n = 402

True also for high FLIPI patients !!

With permission from ASH, Sebban C, et al., Blood 2006;108(8):2540-2544
FL: Autologous Transplant in the R-era: 1st line setting

**Conclusion**: autologous transplantation is best used at relapse
Autologous vs. Allogeneic Transplant for relapsed/resistant indolent NHL: retrospective comparison

With permission from Annals of Oncology, Hosing et al., Ann Onc 2003; 14:737-744
Case 3: 48 year old housewife

- Stage IIIa FL, grade 1, no bulk, FLIPI low risk

WHAT IS YOUR NEXT STEP?
Case 2: 48 year old housewife

- Stage IIIa, grade 1, FL, no bulk, FLIPI low risk
- W + W for 1 year
- At 1 year FU: PD with liver involvement
- 1994: CVP x 8 : CR
- 1995: mediastinal and abdominal relapse

WHAT IS YOUR NEXT STEP?
Case 2: 48 year old housewife

- Stage IIIa, grade 1, FL, no bulk, FLIPI low risk
- W + W for 1 year
- At 1 year FU: PD with liver involvement
- 1994: CVP x 8 : CR
- 1995: mediastinal and abdominal relapse
- CHOP x 4 + BEAM + PBSCT : CR
- 2011: still in CR
Questions in FL

- Is watch and wait still an option?
- Which is the standard first line treatment?
- What is the role of auto/allo-transplantation?
- What is the role of maintenance?
**Intergroup phase III trial**

**Progression free survival from 2nd randomization**

Subgroups according to induction treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients at risk</th>
<th>Progression free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mabthera</td>
<td>34</td>
<td>median: 42.2 months</td>
</tr>
<tr>
<td>Observation</td>
<td>59</td>
<td>median: 11.6 months</td>
</tr>
</tbody>
</table>

**Progression free survival after R-CHOP**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients at risk</th>
<th>Progression free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mabthera</td>
<td>34</td>
<td>median: 51.9 months</td>
</tr>
<tr>
<td>Observation</td>
<td>55</td>
<td>median: 23.1 months</td>
</tr>
</tbody>
</table>

**Overall Logrank test:**

- CHOP: \( p < 0.0001 \)  
- R-CHOP: \( p = 0.004 \)

**Hazard ratio:**

- CHOP: 0.30
- R-CHOP: 0.54

**PRIMA: Study design**

**INDUCTION**
- Registration
- High tumor burden untreated follicular lymphoma
- 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
- Random 1:1*
- Observation‡
- PD/SD off study

With permission from G.A. Salles; Salles G A et al., J Clin Oncol May 2010 vol.28 no.15-suppl 8004 ASCO Meeting 2010
Primary endpoint (PFS) met at the planned interim analysis

stratified HR=0.50  
95% CI 0.39; 0.64 
$p<.0001$

Patients at risk

<table>
<thead>
<tr>
<th>Rituximab maintenance</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=505</td>
<td>N=513</td>
</tr>
</tbody>
</table>

Progression-free rate

82%  66%

With permission from G.A.Salles; Salles G A, et al., J Clin Oncol May 2010 vol.28 no.15-suppl 8004 ASCO Meeting 2010
Meta-analysis of Rituximab maintenance in Indolent Lymphomas: survival

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance in first remission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ardeshna 2010</td>
<td>0.19</td>
<td>0.61</td>
<td>2.7%</td>
<td>1.21 [0.37, 4.00]</td>
<td></td>
</tr>
<tr>
<td>Hochster 2007</td>
<td>1.5067</td>
<td>1.155</td>
<td>0.8%</td>
<td>4.51 [0.47, 43.40]</td>
<td></td>
</tr>
<tr>
<td>Hochster 2009</td>
<td>-0.51</td>
<td>0.3537</td>
<td>8.1%</td>
<td>0.60 [0.30, 1.20]</td>
<td></td>
</tr>
<tr>
<td>Martinelli 2010</td>
<td>0.073</td>
<td>0.5775</td>
<td>3.0%</td>
<td>1.08 [0.35, 3.34]</td>
<td></td>
</tr>
<tr>
<td>Salles 2010</td>
<td>-0.14</td>
<td>0.27</td>
<td>13.8%</td>
<td>0.87 [0.51, 1.48]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>23.4%</td>
<td>0.86 [0.60, 1.25]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.55, df = 4 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.44)

| Maintenance for relapsed/refractory lymphoma |  |  |  |  |  |
| Forstpointner 2006    | -0.72             | 0.5  | 4.0%   | 0.49 [0.18, 1.30]             |                               |
| Hainsworth 2005       | -0.1526           | 0.2819| 12.7%  | 0.86 [0.49, 1.49]             |                               |
| Martinelli 2010       | -0.624            | 0.304 | 10.9%  | 0.54 [0.30, 0.97]             |                               |
| Pettengell 2010       | -0.13             | 0.25 | 16.1%  | 0.88 [0.54, 1.43]             |                               |
| van Oers 2010         | -0.26             | 0.19 | 27.9%  | 0.70 [0.46, 1.01]             |                               |
| Subtotal (95% CI)     |                   |     | 71.6%  | 0.72 [0.57, 0.91]             |                               |

Heterogeneity: Chi² = 2.60, df = 4 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.80 (P = 0.005)

Total (95% CI)
Heterogeneity: Chi² = 6.85, df = 9 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)
Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.41); I² = 0%

With permission from L. Vidal; Vidal L, et al., ASH Meeting 2010
Zevalin consolidation for FL in 1st remission

**PR cases**

- Two-sided log-rank $P < 0.0001$
- Hazard ratio, 0.304
- 95% CI, 0.213 to 0.434

**CR cases**

- Two-sided log-rank $P = 0.0154$
- Hazard ratio, 0.613
- 95% CI, 0.410 to 0.914

**N.B:** only 59/409 had R-containing induction

Conclusions

- **Watch and wait** if there are no symptoms (or single agent R?)

- **R-CHOP** is NOT the standard first line treatment

- Keep **transplant** for (aggressive) relapse

- **Rituximab** maintenance prolongs survival
First line approach in FL

EVALUATE

Prognosis
- Stage
- FLIPI
- Grade (Gene Expression Profile)

Symptoms
- No
- Mild
- Life / Organ threatening

Patients priority
- Longer Survival
- Better Quality of Life
- Long Remission

CHOOSE AMONG

Watch and Wait

"soft" treatment
- rituximab for 1-2 years
- (R-) chlorambucil / cyclophosphamide
- (R-) fludarabine / 2 CDA
- (R-) bendamustine
- Zevalin

"intensive" treatment
- R-CHOP
- R-CVP
- R-FCM
- R-MCP
- ev. + R-maintenance
- or + Zevalin consolidation

Courtesy of M. Ghielmini; Feuerlein et al., Leuk Lymphoma 2009, Vol. 50 (3), 325:334
Thank you!