Low Grade Lymphoma

John Sweetenham MD
September 28th, 2014
Increasing Incidence of NHL


Age at diagnosis (years)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NHL – Frequency of Subtypes

- Follicular (25%)
- Small lymphocytic (7%)
- MALT-type marginal-zone B-cell (7.5%)
- Nodal-type marginal-zone B-cell (< 2%)
- Lymphoplasmacytic (< 2%)
- Diffuse large B-cell (DLBCL) (30%)
- T- and NK-cell (12%)
- Other subtypes (9%)
- Burkitt (2.5%)

Follicular Lymphoma

- 2nd most common NHL (22%)
- Typically advanced stage at presentation
- Often asymptomatic
- Median survival of about 10 years
- Noncurable with conventional therapy
- Overexpression of Bcl-2
- Transformation to aggressive lymphoma occurs in about 30% of patients
Follicular Lymphoma

Immunophenotype
– CD10, 19, 20, 22, 79a (+)

Cytogenetics
– t(14;18)(q32;q21) occurs in >80% of cases of FL
  • Bcl-2 juxtaposition into the IgH heavy chain locus
BCL-2 accumulation in malignant lymphoma

Chromosome 14

Chromosome 18

$t(14;18)$
Accumulation of BCL-2 inhibits the intrinsic apoptotic pathway.

Chemotherapy, radiotherapy

DNA damage

Cellular DNA damage

p53

DNA damage

PUMA, NOXA

BCL-2

Mitochondria

Cytochrome c

APAF1

Caspase 9

Caspase 3, 6, 7

Apoptosis

Follicular Lymphoma

Grading

– **Grade 1**: 1-5 centroblasts/high-power field
– **Grade 2**: 6-15 centroblasts/high-power field
– **Grade 3**: >15 centroblasts/high-power field
  • **Grade 3a**: >15 centroblasts, but centrocytes are present
  • **Grade 3b**: centroblasts form solid sheets
FL: WHO Grading

Grade 1
<5/hpf

Grade 2
6-15/hpf

Grade 3a
>15/hpf

Sheet

Grade 3b
Management of follicular lymphoma

- Has survival for patients with follicular lymphoma improved?
- Are established prognostic factors helpful in patient management?
- What is optimal first line therapy?
- Is there still a role for watch & wait?
- What is the role for ‘maintenance’ therapy?
- Functional imaging in follicular lymphoma
- Rational targets for therapy of low grade NHL
A View of the Natural History of FL

B-Cell Lymphomas Express Several Antigens That Can Be Targeted

OS of follicular lymphoma patients by diagnosis era
(SEER-9; 1983 to 1999)

FL Grade 1/2 OS (UNMC)

2000–2007 (n = 164)

1990–1999 (n = 172)

1982–1989 (n = 80)

p = .0004

UNMC = University of Nebraska Medical Center.
Courtesy of James O. Armitage, MD.
SWOG FL Treatment Results 1974-2004: OS by Regimen

<table>
<thead>
<tr>
<th>N</th>
<th>No. of Deaths</th>
<th>4-Year Estimated OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>179</td>
<td>18</td>
<td>91</td>
</tr>
<tr>
<td>425</td>
<td>189</td>
<td>79</td>
</tr>
<tr>
<td>356</td>
<td>226</td>
<td>69</td>
</tr>
</tbody>
</table>

Meta-Analysis of Survival Benefit of Combination Chemoimmunotherapy in NHL: Overall Survival by Total Groups

<table>
<thead>
<tr>
<th>Trial</th>
<th>HR (95% CI)</th>
<th>Weight (%)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenz 2005</td>
<td>4.11</td>
<td></td>
<td>0.96</td>
</tr>
<tr>
<td>Baez 2005</td>
<td>6.90</td>
<td></td>
<td>0.96</td>
</tr>
<tr>
<td>Forstpointner 2005</td>
<td>16.10</td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>Marcus 2005</td>
<td>15.10</td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Herold 2005</td>
<td>28.92</td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>Hiddeman 2005</td>
<td>28.86</td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.00</td>
<td></td>
<td>0.62</td>
</tr>
</tbody>
</table>

Total events: 100/760 Favors R + Chemo, 143/718 Favors Chemo

Test for heterogeneity: (P=0.60), I² = 0%

Management of follicular lymphoma

• Has survival for patients with follicular lymphoma improved?
• Are established prognostic factors helpful in patient management?
Follicular Lymphoma International Prognostic Index (FLIPI)

• Criteria
• Nodal sites (≤ 4 vs. > 4)
• LDH (≤ normal vs. > normal)
• Age (≤ 60 vs. > 60 years)
• Stage (I or II vs. III or IV)
• Hemoglobin (≥ 12 g/dL vs. < 12 g/dL)

FLIPI nodal map

Cervical
- Pre-auricular
- Upper cervical
- Median or lower cervical
- Posterior cervical
- Supraclavicular

Mediastinal
- Paratracheal
- Mediastinal
- Hilar
- Retrocrural

Axillary
- Axillary

Mesenteric
- Celiac
- Splenic (hepatic) hilar
- Portal
- Mesenteric

Inguinal
- Inguinal
- Femoral

Others: Epitrochlear, popliteal

FLIPI survival probability (%)

\[ p < .0001 \]

Time (months)

Low risk
Intermediate risk
High risk
Revalidation of FLIPI in Patients With Follicular Lymphoma Treated With R-Chemo: OS by FLIPI

- Median follow-up of 26 months; 3.9% (41) deceased
- Insufficient events for OS analysis

“FLIPI – 2”

- Nodal sites (≤ 4 vs. > 4)
- Longest lymph node diameter >6cm
- LDH (≤ normal vs. > normal)
- B₂ microglobulin (≤ normal vs. > normal)
- Age (≤ 60 vs. > 60 years)
- Stage (I or II vs. III or IV)
- Bone marrow involvement
- Hemoglobin (≥ 12 g/dL vs. < 12 g/dL)

Federico et al, JCO 2009 Epub ahead of print
Prognosis in FL Correlated With Gene Expression Patterns in Tumor-Infiltrating Normal Immune Cells

OS based on lymphoma associated macrophage content

Prognostic value of regulatory T-cells, lymphoma associated macrophages and MUM-1 expression in follicular lymphoma treated before and after the introduction of monoclonal antibody therapy: A Southwest Oncology Group study

Sweetenham et al, Ann Oncol 2009
Management of follicular lymphoma

• Has survival for patients with follicular lymphoma improved?
• Are established prognostic factors helpful in patient management?
• What is optimal first line therapy?
## Initial Treatment for Non-Localized FL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watch and Wait</td>
<td>CVP-R</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CHOP-R</td>
</tr>
<tr>
<td>Radioantibody</td>
<td>B-R</td>
</tr>
<tr>
<td>Chlorambucil + R</td>
<td>F-R</td>
</tr>
</tbody>
</table>

Clinical Trial

NCCN, 2011.
Most Common Front-Line Regimens in the US

- Clinical trial: 6.1%
- Observation: 17.7%
- Radiotherapy: 5.6%
- Rituximab monotherapy: 13.9%
- Chemotherapy + rituximab: 51.9%
- Chemotherapy: 3.2%
- Other: 1.6%

Friedberg et al, 2009.
Criteria for Initiation of Treatment: Indolent NHL

**GELF**
- ≥ 3 nodal sites each with diameter ≥ 3 cm
- Any nodal / extranodal mass with diameter ≥ 7 cm
- B symptoms (fevers, night sweats, weight loss)
- Enlarged spleen
- Pleural effusions / ascites
- WBC < 1.0 x 10⁹/L or platelets < 100 x 10⁹/L
- Leukemia (> 5.0 x 10⁹/L malignant cells)

**NCCN**
- GELF criteria
- Symptoms (fatigue, pain, fevers ...)
- Threatened end-organ function / compressive syndrome
- Steady progression
- Elevated LDH or β2-microglobulin
- Patient preference

Observation Vs. Single-Agent Rituximab

- Stage II–IV
- Asymptomatic
- Non-bulky
- Low grade FL

Rituximab vs Watch and Wait
Stage II-IV Asymptomatic Non-Bulky FL


<table>
<thead>
<tr>
<th></th>
<th>Observe (n = 186)</th>
<th>(R \times 4) (n = 84)</th>
<th>(R \times 4 + RM) (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR / PR (%)</td>
<td>3/6</td>
<td>45/33</td>
<td>49/36</td>
</tr>
<tr>
<td>PFS</td>
<td>30%</td>
<td>60%</td>
<td>80%</td>
</tr>
<tr>
<td>TNT</td>
<td>33 mo</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

- PFS Hazard Ratio
  - \(R \text{ vs } W + W\): 0.46, \(P < 0.001\)
  - \(R + M \text{ vs } W + W\): 0.21, \(P < 0.001\)
  - \(R + M \text{ vs } R\): 0.43, \(P = 0.001\)
- Improved TTNT in the R arms
  - 33 mo vs NR at 4 yr (\(P < 0.001\))
- No difference in OS (\(P > 0.5\))
- Quality of life no worse

\(\text{Observe } n = 186\)
\(R \times 4\) \(n = 84\)
\(R \times 4 + RM\) \(n = 192\)

\(\text{PFS}\)

\(\text{TNT}\)

\(\text{Progression-Free Survival}\)

\(\text{Proportion of Patients Progression Free}\)

\(0.1\)
\(0.2\)
\(0.3\)
\(0.4\)
\(0.5\)
\(0.6\)
\(0.7\)
\(0.8\)
\(0.9\)
\(1.0\)

\(0\)
\(1\)
\(2\)
\(3\)
\(4\)
\(5\)

\(\text{W + W}\)
\(\text{R4}\)
\(\text{R4 + RM}\)
Bendamustine-Rituximab (B-R) vs CHOP-R

StiL NHL 1-2003

Bendamustine 90 mg/m² day 1+2 + R day 1, max 6 cycles, q 4 wks.
CHOP-R, max 6 cycles, q 3 wks.
**Bendamustine + Rituximab (BR) vs R-CHOP in Untreated Indolent and MCL**

**PFS: Follicular Lymphoma (n = 279)**

<table>
<thead>
<tr>
<th>Response</th>
<th>BR, n = 166</th>
<th>R-CHOP, n = 149</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>93</td>
<td>91</td>
<td>--</td>
</tr>
<tr>
<td>CR, %</td>
<td>40</td>
<td>30</td>
<td>0.021</td>
</tr>
<tr>
<td>PFS, months</td>
<td>69.5</td>
<td>31</td>
<td>0.000015</td>
</tr>
<tr>
<td>PFS for FL, months</td>
<td>NR</td>
<td>41</td>
<td>0.0072</td>
</tr>
<tr>
<td>PFS, FLIPI low (1 or 2)</td>
<td>NR</td>
<td>47</td>
<td>0.0428</td>
</tr>
<tr>
<td>PFS, FLIPI high (3-5)</td>
<td>53</td>
<td>35</td>
<td>0.0679</td>
</tr>
<tr>
<td>7-year OS, %</td>
<td>76</td>
<td>59.5</td>
<td>--</td>
</tr>
</tbody>
</table>

Hazard Ratio, 0.61 (95% CI 0.42-0.87)

P = 0.0072
Untreated High Risk Follicular Lymphoma: E2408 Study Schema

**BIONIC: Bortezomib Induction Or Novel Continue**

---

**Induction**
- R-CHOP x 6 q21 days
- RB-CHOP x 6 q21 days
- R-CHOP x 6 q21 days

**Continuation**
- Rituximab 1 infusion q 2 mo x 2 yr
- Rituximab 1 infusion q 2 mo x 2 yr
- Rituximab 1 infusion q 2 mo x 2 yr
- Lenalidomide 20 mg d1-21 q 28 d x 1 yr

---

**High Risk Follicular Lymphoma**
(FLIPI score 3-5 or GELF high tumor burden)

---

**RANDOMIZE**

---
Study design. *Up to 8 cycles at investigator discretion; B, bendamustine; C, cyclophosphamide; D, doxorubicin; P, prednisone; R, rituximab; V, vincristine.

Flinn I W et al. Blood 2014;123:2944-2952

©2014 by American Society of Hematology
CR-rate ratios with 95% CIs. CR-rate ratio and P value for a Sup test are calculated using the Cochran–Mantel–Haenszel test stratified by predetermined standard treatment and lymphoma type (mantle cell vs other types).
Management of follicular lymphoma

• Has survival for patients with follicular lymphoma improved?
• Are established prognostic factors helpful in patient management?
• What is optimal first line therapy?
• What is the role for ‘maintenance’ therapy?
Phase III RESORT Trial (ECOG E4402) Maintenance Rituximab vs Rituximab Retreatment

**Indolent NHL**
Untreated, low tumor burden, stage III/IV, ECOG PS 0, 1
N = 545

**Rituximab**
375 mg/m² weekly x 4

**PR CR**

**Rituximab scheduled**
q13wk, continue until PD

**Rituximab retreatment**
For PD only, weekly x 4

**FL, n = 384**

**FL, n = 274**

**TIME TO TREATMENT FAILURE**
(1° Endpoint)

**TIME TO 1ST CYTOTOXIC THERAPY**

GELA PRIMA Phase III Study: Rituximab Maintenance in FL

Patients with previously untreated grade 1-3 FL (N = 1200)

- Primary endpoint: PFS
- Secondary endpoints: EFS, OS

CHOP x 6 + Rituximab x 8

CVP x 8 + Rituximab x 8

FCM x 6 + Rituximab x 8

CR, PR

Maintenance Rituximab 375 mg/m² q2m x 2 yrs

Observation

PRIMA Trial: PFS

Stratified HR: 0.50
95% CI: 0.39-0.64
P < 0.0001

Rituximab maintenance (n = 505)
Observation (n = 513)

PRIMA study update

Salles et al, ASH 2013

HR = 0.57
P < 0.0001

6-year PFS = 59.2%
6-year PFS = 42.7%

Median Follow-up: 73 months
PRIMA study update

- PFS benefit was seen regardless of induction therapy or FLIPI score
- No difference in rate of histologic transformation
- No difference in response rate to 2\textsuperscript{nd} line therapy according to arm
- No difference in overall survival

Salles et al, ASH 2013
FIT Study Schema

Start of study

\[ ^{90}\text{Y}-\text{ibritumomab} \quad (n = 208) \]
Rituximab 250 mg/m\(^2\) IV day -7 and day 0 +
\[ ^{90}\text{Y} \quad 14.8 \text{ MBq/kg} \]
(max 1184 MBq/kg)
day 0

CONSOLIDATION

INDUCTION

First-line therapy with CVP, CHOP / CHOP-like, fludarabine combinations, chlorambucil, or rituximab combination

<table>
<thead>
<tr>
<th>CR / CRu or PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of study</td>
</tr>
<tr>
<td>RANDOMIZATION</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No inclusion</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>No further treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 206)</td>
</tr>
</tbody>
</table>

CONTROL

NR
PD
Consolidation RIT in the FIT Trial: Median PFS in All Patients*

*Median observation period: 3.5 years.

Consolidation with $^{90}$ ibrutumomab tiuxetan vs rituximab in follicular lymphoma

- 124 of 146 patients achieving CR after R-CHOP randomized to rituximab vs IT
- Median follow up = 36 months
- PFS = 63% for IT vs 77% for rituximab (HR = 0.517, p = 0.044)
- Higher infection rate in rituximab arm (13 vs 2)
- No difference in overall survival

Lopez-Guillermo et al, ASH 2013
(A) Progression-free and (B) overall survival of 532 patients with advanced-stage follicular lymphoma randomly assigned to either six cycles of cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (CHOP-R) or six cycles of cyclophosphamide,...
Management of follicular lymphoma

• Has survival for patients with follicular lymphoma improved?
• Are established prognostic factors helpful in patient management?
• What is optimal first line therapy?
• Is there still a role for watch & wait?
• What is the role for ‘maintenance’ therapy?
• Functional imaging in follicular lymphoma
Progression-free survival in 202 patients with follicular lymphoma according to post-induction positron emission tomography.

Management of follicular lymphoma

• Has survival for patients with follicular lymphoma improved?
• Are established prognostic factors helpful in patient management?
• What is optimal first line therapy?
• Is there still a role for watch & wait?
• What is the role for ‘maintenance’ therapy?
• Functional imaging in follicular lymphoma
• Rational Targets for therapy in follicular lymphoma
Two Different Modes of B Cell Receptor Signaling
Role of Syk and Modulation of BCR Signaling

Tonic BCR signaling requires Syk expression and activity (phosphorylation)
# B-cell NHL Phase 2 Responses

<table>
<thead>
<tr>
<th></th>
<th>DLBCL patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>23</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>PFS (mo) median (range)</strong></td>
<td>2.7 (0.9, 16.3)</td>
</tr>
<tr>
<td><strong>Time to first resp. (m) median (range)</strong></td>
<td>1.9 (1.8, 4.7)</td>
</tr>
</tbody>
</table>

Bar chart showing % change from screening for different lymphoma subtypes.
Ibrutinib: A First-in-Class Inhibitor of BTK

- Forms covalent bond with cysteine-481 in BTK
- High BTK specificity
- $IC_{50} = 0.5$ nM
- Daily oral dosing produces 24-hr BTK inhibition
- Blocks NF-κB activation in DLBCL cell lines$^{1,2}$
Two Different Modes of B Cell Receptor Signaling
Idelalisib in indolent lymphoma refractory to rituximab and alkylating agents

(N = 125) ORR 57%

aCriterion for lymphadenopathy response [Cheson 2007]
b2 subjects NE, no post baseline evaluation

Gopal et al, ASH 2013
Questions?