Follicular and Marginal Zone Lymphoma Biology and Management
Outline

Epidemiology
Initial Work-up
Prognostic Index
Treatment of Follicular Lymphoma:
- Limited Stage
- Advanced Stage
Frontline: Stil, BRIGHT
Consolidation: PRIMA (Rituximab), FIT (RIT)
Relapse: GADOLIN, Idelalisib, HSCT
Marginal Zone: MALT, Splenic, Nodal
Lymphoplasmacytic Lymphoma
Transformed Lymphoma
NHL Etiology

- Immune deficiency (Congenital or Acquired)
- Autoimmune disorders (e.g. Hashimoto’s thyroiditis, Sjogren’s syndrome, RA)
- Infectious agents
  - HIV
  - Helicobacter pylori (infection of stomach and MALT)
  - EBV, Human T-cell leukemia virus, KS-associated Herpes virus
- Chemical and physical agents (e.g. pesticides)
- Dietary
Non-Hodgkin Lymphoma

WHO Classification (2016) of Lymphoid Neoplasms (indolent NHL)

Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

<table>
<thead>
<tr>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mature B-cell neoplasms</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma</td>
</tr>
<tr>
<td>Monoclonal B-cell lymphocytosis*</td>
</tr>
<tr>
<td>B-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>Splenic marginal zone lymphoma</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
</tr>
<tr>
<td>Splenic B-cell lymphoma/leukemia, unclassifiable</td>
</tr>
<tr>
<td>Splenic diffuse red pulp small B-cell lymphoma</td>
</tr>
<tr>
<td>Hairy cell leukemia-variant</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
</tr>
<tr>
<td>Monoclonal gammopathy of undetermined significance (MGUS), IgM*</td>
</tr>
<tr>
<td>( \mu ) heavy-chain disease</td>
</tr>
<tr>
<td>( \gamma ) heavy-chain disease</td>
</tr>
<tr>
<td>( \alpha ) heavy-chain disease</td>
</tr>
<tr>
<td>Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*</td>
</tr>
<tr>
<td>Plasma cell myeloma</td>
</tr>
<tr>
<td>Solitary plasmacytoma of bone</td>
</tr>
<tr>
<td>Extrasosseous plasmacytoma</td>
</tr>
<tr>
<td>Monoclonal immunoglobulin deposition diseases*</td>
</tr>
<tr>
<td>Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue</td>
</tr>
<tr>
<td>(MALT lymphoma)</td>
</tr>
<tr>
<td>Nodal marginal zone lymphoma</td>
</tr>
<tr>
<td>Pediatric nodal marginal zone lymphoma</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>In situ follicular neoplasia*</td>
</tr>
<tr>
<td>Duodenal-type follicular lymphoma*</td>
</tr>
<tr>
<td>Pediatric-type follicular lymphoma*</td>
</tr>
<tr>
<td>Large B-cell lymphoma with IRF4 rearrangement*</td>
</tr>
<tr>
<td>Primary cutaneous follicle center lymphoma</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>In situ mantle cell neoplasia*</td>
</tr>
</tbody>
</table>

Swerdlow, Blood 2016

* Change from 2008
Initial Workup

- History and Physical: B symptoms
- LN Biopsy: excisional, core, FNA
- Laboratory: CBC, Chem, LDH, B2M
- Hep B, hep C, HIV
- CT scans C/A/P with contrast
- PET scan
- Bone Marrow Biopsy: Flow, IHC, FISH, Cytogenetics
- MUGA, Echocardiogram
- MRI, LP if indicated

B symptoms: Fever, drenching night sweats, > 10% unintentional weight loss in 6 months
## Non-Hodgkin’s Lymphomas of Small Mature B-cells Immunophenotype

<table>
<thead>
<tr>
<th></th>
<th>SLL</th>
<th>LPL</th>
<th>MZL</th>
<th>FL</th>
<th>MCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ig</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD5</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD23</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>CD25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>CD103</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Costwolds Modification of Ann Arbor Staging System
Reactive lymph node with follicular hyperplasia

H&E  CD20  CD3
Follicular Lymphoma Morphology
Follicular Lymphoma Grading

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5 Centroblasts per high power field</td>
<td>6-15</td>
<td>&gt;15</td>
</tr>
</tbody>
</table>
Follicular Lymphoma
\( t(14;18)(q32;q21) \)
Bcl-2 staining

Reactive Lymph node

Follicular Lymphoma

90% of Follicular Lymphomas.
20% of Diffuse Large B-cell Lymphomas
Chromosomal translocations in indolent NHL

T(14;18)(q32;q21)  Follicular Lymphoma
T(11;18)(q21;q21)  MALT Lymphoma
T(14;18)(q32;q21)  MALT Lymphoma
T(1;14)(q22;q32)  MALT Lymphoma
T(3;14)(p14.1;q32)  MALT Lymphoma
T(11;14)(q13;q32)  Mantle cell Lymphoma
Marginal Zone B-cell Lymphoma

Gastric mucosa

Infiltration of lamina propria and muscularis mucosa

Lymph Node
MALT Lymphoma with t(11;18)(q21;q21)
MALT Lymphoma with \( t(14;18)(q32;q21) \)
MALT Lymphoma
Common sites and associations

- Stomach
- Small bowel
- Thyroid
- Parotid
- Lung
- Skin
- Ocular

- H. Pylori
- C. Jejuni
- Hashimoto thyroiditis
- Sjogren syndrome
- Sjogren syndrome
- B. Burgdorferi
- Chlamydia psittaci
Follicular Lymphoma International Prognostic Index (FLIPI-1)

FLIPI (No-LASH):
- **Nb** of involved **nodal** areas >4
- **LDH** > ULN
- Age > 60
- Stage III-IV
- Hemoglobin < 12 g/L

<table>
<thead>
<tr>
<th>Risk model</th>
<th>No. of factors</th>
<th>Distribution of cases (%)</th>
<th>5-year OS (%)</th>
<th>10-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>36</td>
<td>91</td>
<td>71</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>37</td>
<td>78</td>
<td>51</td>
</tr>
<tr>
<td>High</td>
<td>≥3</td>
<td>27</td>
<td>53</td>
<td>36</td>
</tr>
</tbody>
</table>

Follicular Lymphoma International Prognostic Index 2 (FLIPI-2)

- Longest diameter of largest involved node > 6 cm
- Bone marrow involvement
- Age > 60
- β2-macroglobulin > ULN
- Hemoglobin < 12 g/L

<table>
<thead>
<tr>
<th>Risk model</th>
<th>No. of factors</th>
<th>Distribution of cases (%)</th>
<th>3-year PFS (%)</th>
<th>5-year PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>20</td>
<td>91</td>
<td>79</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>53</td>
<td>69</td>
<td>51</td>
</tr>
<tr>
<td>High</td>
<td>≥3</td>
<td>27</td>
<td>51</td>
<td>18</td>
</tr>
</tbody>
</table>

**NCCN Guidelines Version 2.2017**

**Follicular Lymphoma (grade 1-2)**

**GELF CRITERIA**
- Involvement of ≥3 nodal sites, each with a diameter of ≥3 cm
- Any nodal or extranodal tumor mass with a diameter of ≥7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes <1.0 x 10^9/L and/or platelets <100 x 10^9/L)
- Leukemia (>5.0 x 10^9/L malignant cells)

**FLIPI - 1 CRITERIA**
- **Age**: ≥60 y
- **Ann Arbor stage**: III-IV
- **Hemoglobin level**: <12 g/dL
- **Serum LDH level**: >ULN (upper limit of normal)
- **Number of nodal sites**: ≥5

<table>
<thead>
<tr>
<th>Risk group according to FLIPI chart</th>
<th>Number of factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0–1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>≥3</td>
</tr>
</tbody>
</table>

© 2007 Dana-Farber Cancer Institute, Inc. All rights reserved. Permission is hereby granted for copying this image by photocopy or similar process for use in the practice of medicine or for research purposes. No other use is permitted which will infringe the copyright without the express written consent of Dana-Farber Cancer Institute, Inc.

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

© 2017 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.
## Considerations for Choosing Therapy

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Disease Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age</td>
<td>- Stage</td>
</tr>
<tr>
<td>- Symptoms</td>
<td>- Grade</td>
</tr>
<tr>
<td>- Short &amp; long term goals</td>
<td>- transformation</td>
</tr>
<tr>
<td>- Co-morbidity</td>
<td>- Sites of involvement</td>
</tr>
<tr>
<td>- Preserve future options</td>
<td>- Prior therapy</td>
</tr>
<tr>
<td></td>
<td>- Time from prior therapy</td>
</tr>
<tr>
<td></td>
<td>- Prognostic factors</td>
</tr>
</tbody>
</table>

Grade 3 is an area of controversy. Grade 3b is commonly treated as DLBCL.
Limited Stage indolent NHL

- Local RT has the potential for cure or very prolonged remission
- Median disease free interval close to 10 years.
- Median survival of 17 years.
- Role of chemo-immunotherapy with IFRT: 10-year PFS 59 vs 41%.
- Observation
Advanced Stage indolent NHL

- Incurable with conventional therapy
- Older patients with co-morbidities
- Observation
- Response duration is usually shorter with each course of “similar” therapy
- Rituximab weekly x 4 for low tumor burden. RESORT trial
- Chemo-immunotherapy (category 1):
  - BR
  - RCHOP
  - RCVP
Advanced Stage indolent NHL

Historical approach:
- Watch and Wait (Worry): asymptomatic patients
- Alkylating Agents +/- steroids: “old standard”
- CVP: ORR 50-70%, CR 15-20%
- CHOP: Higher ORR, no increase in OS
- Fludara: ORR 68%, CR 38%, No increase in OS
- Fludarabine combination chemo: Higher ORR, CR, but no increase in OS

Current approach:
- Chemo-immunotherapy: bendamustine, anti-CD20, RIT
- Maintenance: anti-CD20 (rituximab q 2 months for 2 years)

Future approach:
Chemo-free regimens: Revlimid and Rituximab
Rituxan-based combination chemotherapy in FL

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVP</strong></td>
<td>64% 87% <em>(p&lt;0.011)</em></td>
<td>14 months 38 months <em>(p&lt;0.0001)</em></td>
<td>83% 89% <em>(p&lt;0.022)</em></td>
</tr>
<tr>
<td><strong>R-CVP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHOP</strong></td>
<td>90% 96% <em>(p&lt;0.011)</em></td>
<td>31 months N.R. <em>(p&lt;0.0006)</em></td>
<td>90% 95% <em>(p&lt;0.016)</em></td>
</tr>
<tr>
<td><strong>R-CHOP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MCP</strong></td>
<td>75% 92% <em>(p&lt;0.0009)</em></td>
<td>26 months N.R. <em>(p&lt;0.0001)</em></td>
<td>74% 87% <em>(p&lt;0.0096)</em></td>
</tr>
<tr>
<td><strong>R-MCP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHVP+IFN</strong></td>
<td>72% 81% <em>(p&lt;0.0001)</em></td>
<td>35 months N.R. <em>(p&lt;0.0001)</em></td>
<td>79% 84% <em>(p&lt;0.029)</em></td>
</tr>
<tr>
<td><strong>R-CHVP+IFN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Improvement in OS for FL

Era 1: pre-anthracycline (1960-1975)

Lymphocare Study

A. Initial Treatment - All Patients
- Clinical trial: 6.1%
- Other: 1.6%
- Observation: 17.7%
- Chemotherapy: 3.2%
- Radiotherapy: 5.6%
- Rituximab monotherapy: 13.9%
- Chemotherapy + rituximab: 51.9%

B. Initial Treatment - Stage I Patients
- Chemotherapy: 2.5%
- Other: 2.1%
- Observation: 28.7%
- Chemotherapy + rituximab: 30.4%
- Radiotherapy: 23.4%
- Rituximab monotherapy: 12.9%

Stil: BR vs R-CHOP in frontline iNHL

- HR 0.58 (95% CI 0.44 - 0.74)
- p<0.0001

- Median (IQR; months)
  - B-R 69.5 (26.1 to not yet reached)
  - R-CHOP 31.2 (15.2 - 65.7)

Number at risk:
- B-R: 207, 169, 125, 71, 35, 19
- R-CHOP: 185, 123, 83, 54, 24, 9

Figure 2: Progression-free survival

B-R = bendamustine plus rituximab. R-CHOP = CHOP plus rituximab.

BRIGHT: BR vs R-CHOP/R-CVP in frontline FL

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>BR</th>
<th>R-CHOP/R-CVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>97%</td>
<td>91%</td>
</tr>
<tr>
<td>Complete response</td>
<td>31%</td>
<td>25%</td>
</tr>
<tr>
<td>Partial response</td>
<td>65%</td>
<td>66%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>BR</th>
<th>R-CHOP</th>
<th>R-CVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>63%</td>
<td>58%</td>
<td>39%</td>
</tr>
<tr>
<td>Opportunistic infection</td>
<td>10-12%</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Rash</td>
<td>20-24%</td>
<td>12%</td>
<td>16%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>9-14%</td>
<td>44%</td>
<td>47%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3-4%</td>
<td>51%</td>
<td>21%</td>
</tr>
<tr>
<td>Neutropenia (Gr3+)</td>
<td>39-49%</td>
<td>87%</td>
<td>56%</td>
</tr>
<tr>
<td>Lymphopenia (Gr3+)</td>
<td>61-63%</td>
<td>33%</td>
<td>28%</td>
</tr>
<tr>
<td>Platelets (Gr3+)</td>
<td>5-10%</td>
<td>12%</td>
<td>2%</td>
</tr>
</tbody>
</table>

PRIMA: Maintenance Rituxan in frontline FL

FIT (Front-line Indolent trial)

Induction

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

- Not reached
- Progressive disease

Start of Study

- Complete response
- Unconfirmed complete response
- Partial response

Consolidation

- Rituximab 250 mg/m² IV day -7 and day 0 + ⁹⁰Y-ibrutinumomab tiuxetan 14.8 MBq/kg (max 1,148 MBq/kg) day 0
- Control
- No additional treatment

Random Assignment
FIT (Front-line Indolent trial)

Two-sided log-rank $P < .0001$
Hazard ratio, 0.465
95% CI, 0.357 to 0.605

$^{90}$Y-ibritumomab tiuxetan (n = 208):
Median, 36.5 months

Control (n = 206):
Median, 13.3 months

RIT of B-cell Lymphoma

Y 90-Ibritumomab tiuxetan (Zevalin)
Tositumomab I-131 (Bexxar)*
Activity: Upfront LGL > relapsed LGL > transformed
RIT more effective in:
- Tumors ≤ 5 cm
- Non-bulky disease
- Chemosensitive disease
MDS/Secondary AML: “Low” incidence

* Discontinued in 2-2014 due to decline in usage
Poor Outcomes for Early Relapse after Chemoimmunotherapy in FL
NCCN: Treatment options at relapse

Antracycline if not given previously
Rituximab alone or in combination
Bendamustine + obinutuzumab
Radioimmunotherapy (category 1)
Radiation
HSCT: autologous, allogeneic
Idelalisib (refractory to both alkylator and rituximab)
Lenalidomide rituximab
Investigational agents
Anti-CD20 Monoclonal Antibodies

A
- Distinct 3D binding to CD20
- Glyco-engineered Fc region

B
- Antibody-dependent cellular cytotoxicity (ADCC)
- Complement-mediated cytotoxicity (CMC)

Obinutuzumab (Type 2)

Rituximab (Type 1)

B-cell NHL

Direct apoptosis

Lipid rafts

VCUHealth
GADOLIN: Benda+Obi vs Benda in Rituximab-refractory i-NHL

HSCT in FL

**Autologous SCT:**
- Not indicated as consolidation in CR1
- In the relapsed setting:
  - FLIPI High
  - ≥ 3 chemo regimens
  - FL 3 (vs. FL1/2)
  - Transformation to large cell

**Allogeneic HCT is only known cure**
- Benefit vs TRM

Auto & Allo SCT in FL

Sweden: N=904 FL pts undergoing SCT
A. 176 (19%) = allogeneic
B. 131 (14%) = purged autologous
C. 597 (67%) = unpurged autologous
5 years TRM: 30%, 14% and 8% for A, B, C.
5 years recurrence rates: 21%, 43% and 58%
5 years survival: 51%, 62% and 55%

MDACC: N=47 FL pts. 8-yr experience of non-myeloablative, med F/U=60m; OS 85%, PFS 83%
Targeted Therapy in i-NHL

Benefits:
Less non-specific toxicities
Targeting resistance pathways: Bcl-2 (Venetoclax)
Non-cross resistance MOA
Additive/synergistic activity
Targets for Novel agents in Lymphoma

Cell proliferation, growth and survival

Idelalisib
IPI-145

ABT-199
Obatoclax

Ibrutinib
Enzastaurin

Bortezomib
Carfilzomib

Bcl-2
Mcl-1

NFAT activation
MAP kinase activation
mTOR activation

Everolimus
Temsirolimus
Rapamycin

VCU Health

FDA Approved Targeted Agents

Obinutuzumab & Chlorambucil

Idelalisib & Rituxan

Brentuximab Vedotin (CD30-ADC)

Pralatrexate (Antifolate)

Belinostat (HDACI)

Romidepsin (HDACI)

Vorinostat (HDACI)

Denileukin difitox (Diphtheria toxin-IL-2)

Lenalidomide (IMID)

Bortezomib (Protasome Inhibitor)

Idelalisib (PI3K inhibitor)

Idelalisib (PI3K inhibitor)

Ibrutinib (BTK inhibitor)

Ibrutinib (BTK inhibitor)

Ibrutinib (BTK inhibitor)

Ibrutinib (BTK inhibitor)

Bortezomib (Protasome Inhibitor)

Other

Overall Response Rate (%)

Yazbeck V and Grant S. Expert Opinion on Investigational Drugs 2015
Idelalisib in Relapsed and refractory i-NHL
# Idelalisib in Relapsed and refractory i-NHL

<table>
<thead>
<tr>
<th>Outcomes, %</th>
<th>FL</th>
<th>SLL</th>
<th>MZL</th>
<th>LPL/WM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>56</td>
<td>61</td>
<td>47</td>
<td>80</td>
</tr>
<tr>
<td>CR</td>
<td>14</td>
<td>4</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>42</td>
<td>57</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>SD</td>
<td>32</td>
<td>36</td>
<td>47</td>
<td>10</td>
</tr>
<tr>
<td>PD</td>
<td>8</td>
<td>0</td>
<td>7</td>
<td>10</td>
</tr>
</tbody>
</table>

Extranodal Marginal Zone Lymphoma of MALT Type

Immunophenotype:
- Positive for Slg and B-cell antigens (CD19, CD20, CD22)
- Negative for CD5 and CD10

Clinical features:
- Present with a mass
- Many patients have underlying autoimmune or inflammatory process:
  Helicobacter pylori gastritis = Gastric MALT
  Hashimoto’s thyroiditis = Thyroid MALT
  Sjogren’s syndrome = Salivary gland MALT
- May undergo transformation to DLBCL (<10%, late)
- Favorable outcome: 5 years OS~90%
Gastric MALT Lymphoma

- Most common presentation of MALT lymphoma
- Common presentation: Dyspepsia or vague upper GI sx’s
- Usual endoscopic findings: ulcer, gastritis, gastric thickening
- When localized to stomach: often associated with H. pylori
- Successful eradication of H. pylori = CR in 2/3 of patients
- Typically combination of antibiotics (e.g. clarithromycin, amoxicillin, metronidazole) plus proton pump inhibitor (e.g. omeprazole) x 14 days
- Neg for H. pylori or if positive for t(11;18), t(1;14), or t(14;18): Unresponsive to antibiotics… Consider alternative Rx
- Alternative Rx: RT (30-33 Gy), surgery, rituximab, immunochemotherapy
- After Rx: repeat endoscopy after 3m, then prn
Splenic Marginal Zone Lymphoma

Clinical Features:
- Symptomatic splenomegaly: Typical presentation
- Peripheral lymphadenopathy: Uncommon
- Bone marrow involvement: Frequent found (~90%)

Monoclonal gammopathy: Approximately 50% (mainly IgM)
Evaluate and r/o Hepatitis C viral infection. If”+” Hepatology csIt

Therapy:
- Asymptomatic: monitor off-therapy
- Splenectomy: 1st-line therapy (i.e. symptomatic splenomegaly +/- cytopenia)
- Alternative: Splenic RT, chemo, rituximab +/- chemo

VCU Health
Nodal Marginal Zone Lymphoma

“Nodal equivalent” of MALT lymphoma
Rare and often occurs as spread from extranodal MALT

Clinical Features:
- Often presents as LA (neck and ingunal areas)
- May be associated with: hepatitis C; Sjogren syndrome or other autoimmune disorders
- Distinctive characteristic: Co-existence of other NHL histologies
- Typical: Indolent nature and without systemic symptoms

Therapy:
- Similar to FL
Lymphoplasmacytic Lymphoma

Morphology:
- Mature small lymphocytes with plasmacytoid differentiation (admixed with variable numbers of plasma cells and immunoblasts)

Immunophenotype:
- CD19+, CD20+; usually CD5-; sIg+ (moderate)
- Intracellular Ig (usually IgM) on paraffin immunoperoxidase

Clinical features:
- LA (15%), SPM (15%), HPM (20%), lymphocytosis (30%), anemia, possible neurologic findings.
Lymphoplasmacytic Lymphoma

Clinical Features:
- When associated with an elevated serum monoclonal IgM = waldenstrom’s Macroglobulinemia
High IgM levels:
Hyperviscosity Syndrome (~15%)
Fatigue, MS changes, HA, blurred vision, mucosal bleeding (immediate plasmapheresis)
IgM may have RF activity and/or function as cryoglobulin
- Chromosomal t(9;14) : Seen in 50% of patients

Therapy:
- Alkylating agent +/- steroids; nucleoside analogues; combination chemo +/- rituximab, IMiDs, proteasome inhibitors, ibrutinib.
Ibrutinib in indolent NHL

Cell proliferation, growth and survival

FDA: CLL SLL MCL WM MZL

Transformed Lymphoma

• Low grade lymphoma has a risk of transformation of ~30% at 10 years after initial diagnosis.
• Definition of transformation: DLBCL, Burkitt-like lymphoma
• Patients who develop transformed lymphoma (TL) usually demonstrate an aggressive disease course:
  - 10 year OS of 36% for patients with TL vs 75% for patients with non-TL (P<0.001)
  - 1.7 years median OS for patients with TL, despite increased use of high-dose chemotherapy and stem cell transplantation
• Patients with TL have fewer effective treatment options than de novo DLBCL
• Optimal therapeutic strategy for TL patients has not been well defined
Transformed Lymphoma

Transformation rate ~ 30% at 10 years
Median survival 1-2 years
Transformed FL

I. Multiple prior therapies*
   RIT
   R-chemotherapy
   IF RT
   Clinical trial
   BSC

II. Minimal/No prior therapy**
   R-CHOP

* If PR or CR: consider HDT with ASCT
** If in minimal / no prior therapy group and achieve a “CR”: ok to observe.
Summary: Indolent NHL

Stage I-II

- ~50% long term (10-20 yr) DFS with RT alone (cure)

Stage III-IV

- Remission rate 70-85% with chemo, ~50-70% with rituximab alone, 70-95% with chemo+rituxan
- Rituximab maintenance or RIT consolidation improve PFS not OS
- Cure rate is 0 except allogeneic SCT
- Median OS ~20 years
Follicular Lymphoma
54-year-old man presents with palpable cervical lymphadenopathy. He has a 35-pack-year smoking history. There are no constitutional symptoms. The primary care physician notes a firm 3-cm submandibular mass and refers the patient to otolaryngology. Evaluation of a sample obtained by fine-needle aspiration shows an abundance of lymphocytes that are a mixture of small and large cells, some with cleaved nuclei. On flow cytometry, the cells are CD5\(^-\), CD10\(^+\), and CD20\(^+\). The pathology report indicates the patient has “malignant lymphoma of follicular center cell origin.”
Which of the following is most appropriate information to communicate to patient

- He has follicular lymphoma, and additional tests will be needed to complete staging
- He has follicular lymphoma, and it could be either treated or observed.
- This may be a reactive process mimicking lymphoma, and viral studies are indicated
- The biopsy specimen indicates lymphoma, but an excisional biopsy is needed to determine the exact subtype
Which of the following is most appropriate information to communicate to patient

- He has follicular lymphoma, and additional tests will be needed to complete staging
- He has follicular lymphoma, and it could be either treated or observed.
- This may be a reactive process mimicking lymphoma, and viral studies are indicated
- **The biopsy specimen indicates lymphoma, but an excisional biopsy is needed to determine the exact subtype**
In the current era of minimally invasive procedures, patients with lymphoma often go to a hematologist/oncologist with very small biopsy specimens, including fine-needle aspiration samples. Although flow cytometry can be helpful in narrowing the range of options, management decisions should not be made until exact lymphoma subtyping is completed. This process requires either an excisional lymph node biopsy or several large-bore core needle biopsies, such that lymph node architecture can be ascertained by an expert hematopathologist. In this clinical scenario, it is inappropriate to tell the patient that he has follicular lymphoma. Although follicular lymphoma is likely based on the preliminary information, one cannot say whether it is grade 1-2, grade 3A, or grade 3B. In addition, it is theoretically possible that he has diffuse large B-cell lymphoma. However, it is unlikely to be a reactive process. Treatment and prognosis should not be conveyed until exact subtyping is completed.
Question #2

A 57-year-old man recently completed 6 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for stage III, grade 1-2, high-tumor-burden follicular lymphoma. Positron emission tomography images at the end of therapy indicate complete remission. You initiate a discussion with the patient about maintenance therapy with rituximab.
Which of the following has been achieved with maintenance rituximab in a prospective randomized trial(s)?

- Improved overall survival
- Improved progression-free survival
- Improved quality of life
- Decreased risk for histologic transformation
Question #2 (continued)

Which of the following has been achieved with maintenance rituximab in a prospective randomized trial(s)?

• Improved overall survival
• **Improved progression-free survival**
• Improved quality of life
• Decreased risk for histologic transformation
The PRIMA trial was a large phase 3 study that enrolled patients with previously untreated, high-tumor-burden (by Groupe d’Étude des Lymphomes Folliculaires [GELF] criteria) follicular lymphoma. Most patients received rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as induction therapy, and a minority received rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP) or rituximab plus fludarabine, cyclophosphamide, and mitoxantrone (R-FCM). On completion of induction therapy, patients were randomly assigned to maintenance rituximab (a single dose every 2 months for 2 years) or observation. Progression-free survival was significantly improved for patients assigned to maintenance therapy. To date, no overall survival difference has been demonstrated in this prospective clinical trial. There was no difference in quality of life or risk for transformation between the two arms. Infections were slightly more common in patients assigned to maintenance therapy.
A 77-year-old man has recurrent, progressive, and symptomatic follicular lymphoma. Prior therapies have included rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP) (9 years ago), radioimmunotherapy (5 years ago), single-agent rituximab (2 years ago), and rituximab and bendamustine (1 year ago). As a result of these treatments, he has chronic thrombocytopenia, with a baseline platelet count of $8 \times 10^9$/L (reference range, $150 \times 10^9$-$450 \times 10^9$/L). Evaluation of a recent bone marrow biopsy specimen indicated 20% cellularity and no evidence of myelodysplasia. You discuss treatment options with him, explaining that oral medications are now available for managing lymphoma.
Which of the following is the most appropriate oral medication for this patient?

- Fostamatinib
- Ibrutinib
- Idelalisib
- Imatinib
Which of the following is the most appropriate oral medication for this patient?

• Fostamatinib
• Ibrutinib
• **Idelalisib**
• Imatinib
Targeting the B-cell receptor and its downstream pathways has proven to be a viable strategy in several B-cell lymphoma subtypes. Fostamatinib was the first B-cell receptor pathway inhibitor to show activity in B-cell lymphomas, but it is not approved for therapy and is not being developed further. However, multiple agents are in development. At this point, only idelalisib is approved by the US Food and Drug Administration (FDA) for follicular lymphoma. Idelalisib is an oral phosphoinositide 3-kinase (PI3K) inhibitor specifically targeting the delta isoform of PI3K. In a single-arm trial enrolling patients considered to have disease refractory to both rituximab and an alkylating agent, idelalisib was associated with an objective response rate of 57% and a median response duration of 12.5 months. Major toxicities included neutropenia, diarrhea, and elevated transaminase levels. Ibrutinib has remarkable activity in chronic lymphocytic leukemia (and is FDA approved in that setting) but only modest activity in follicular lymphoma. Imatinib has no significant activity in non-Hodgkin lymphoma.
Marginal Zone Lymphoma
A 62-year-old man presents with progressive abdominal discomfort of several months’ duration. The discomfort is present most of the time, is dull, and is mostly in the left upper quadrant. The primary care physician notes a midabdominal mass. Ultrasonography images show massive splenomegaly, with the spleen measuring approximately 24 cm. Laboratory values include a hemoglobin level of 10.4 g/dL (reference range, 13-17.3 g/dL), a white blood cell count of $12.45 \times 10^9$/L (reference range, $4 \times 10^9$-$10 \times 10^9$/L) with 75% lymphocytes, and a platelet count of $120 \times 10^9$/L (reference range, $150 \times 10^9$-$450 \times 10^9$/L); the lactate dehydrogenase level is normal. A bone marrow specimen is evaluated, and flow cytometry indicates a $\lambda$-restricted B-cell population that is CD5<sup>-</sup>, CD10<sup>-</sup>, CD20<sup>+</sup>, and CD103<sup>-</sup>. Serum protein electrophoresis indicates no monoclonal bands.
Question #1 (continued)

Which of the following findings are characteristic of this disorder?

- Activating mutation in \textit{MYD88}
- \textit{BRAF} V600E mutation
- Balanced translocation between chromosomes 11 and 14
- No characteristic molecular defect
Question #1 (continued)

Which of the following findings are characteristic of this disorder?

- Activating mutation in *MYD88*
- *BRAF* V600E mutation
- Balanced translocation between chromosomes 11 and 14
- **No characteristic molecular defect**
A variety of lymphoid malignancies can present with massive splenomegaly. In this clinical scenario, the most likely diagnosis is splenic marginal zone lymphoma, which is largely a diagnosis of exclusion. The CD5 negativity makes mantle cell lymphoma, a disorder characterized by t(11;14), unlikely. The CD103 negativity makes hairy cell leukemia, a disorder characterized by the \textit{BRAF} V600E mutation, unlikely. The lack of an immunoglobulin M paraprotein makes Waldenström macroglobulinemia, a disorder characterized by activating \textit{MYD88} mutations, unlikely. No characteristic molecular defect has been associated with splenic marginal zone lymphoma.