Management of Follicular Lymphoma

Lymphoma Tumor Board

September 22, 2017
Relative Incidence of NHL Subtypes

>71,000 new cases in US in 2015

- DLBCL: 32%
- FL: 22%
- Composite: 13%
- Burkitt’s-like: 2%
- LPL: 1%
- ALCL: 2%
- PMLBCL: 2%
- MZL: 6%
- PTCL: 6%
- MCL: 6%
- SLL: 6%

NHL = non-Hodgkin lymphoma; FL = follicular lymphoma; DLBCL = diffuse large B-cell lymphoma.
NCCN Guidelines Version 3.2017 Table of Contents

B-cell Lymphomas

NCCN B-cell Lymphoma Panel Members
Summary of the Guidelines Updates

- Follicular Lymphoma (FOLL-1)
- Marginal Zone Lymphomas (MZL-1)
  - Gastric MALT Lymphoma (MALT-1)
  - Nongastric MALT Lymphoma (NGMLT-1)
  - Nodal Marginal Zone Lymphoma (NODE-1)
  - Splenic Marginal Zone Lymphoma (SPLN-1)
- Mantle Cell Lymphoma (MANT-1)
- Diffuse Large B-Cell Lymphoma (BCEL-1)
- Burkitt Lymphoma (BURK-1)
- AIDS-Related B-Cell Lymphomas (AIDS-1)
- Lymphoblastic Lymphoma (BLAST-1)
- Post-Transplant Lymphoproliferative Disorders (PTLD-1)
- Castleman's Disease (CD-1)

Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A)
Supportive Care for B-cell Lymphomas (NHODG-B)
Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C)
Principles of Radiation Therapy (NHODG-D)
Special Considerations for the Use of Small-Molecule Inhibitors (ibrutinib and Idelalisib) (NHODG-E)

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

Classification and Staging (ST-1)

Primary CNS Lymphoma (See NCCN Guidelines for CNS)
Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (See NCCN Guidelines for WM/LPL)

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Indolent Non-Hodgkin Lymphomas

• Slow-growing [typically] B-cell malignancies
• Responsive to initial therapy, yet inevitably recur; incurable with conventional therapy
• Most common subtypes:
  • Follicular lymphoma (FL)
  • Marginal zone lymphoma (MZL)
  • Small lymphocytic lymphoma (SLL) – CLL counterpart
• FL is the 2\textsuperscript{nd} most common subtype of NHL
• FL comprises ~25% of NHL and ~70% of indolent NHL
• FL is a malignancy of follicle center B-cells – CD10\textsuperscript{+}
• Also known as CB/CC lymphoma (Centroblastic/Centrocytic lymphoma), nodular lymphoma, and Brill-Symmers Disease
• Hallmark translocation between chromosomes 14 and 18 [t(14;18)] that results in overexpression of \textit{BCL2}
t(14;18) – Cytogenetic hallmark of FL
Model of FL pathogenesis

Bone marrow

Peripheral Blood

Germinal Centre

Secondary Lymphoid Organs

V(D)J Recombination

BM Niches?

Pre-B

Immature B

Mature Naive B

CD19+20+ IgM+ [t(14;18)]

CD19+20+ IgM+/D+ [t(14;18)]

Ag presentation

Light zone

Mantle zone

Apoptosis

BCL2 Rescue

sigM selection

SHM

CSR

"FL-like"

CD19+27+ IgM+-> IgG+ [CSR+ SHM+ t(14;18)]]

Release

Homing in activated follicles?

2nd HIT

Ag Recall?

Trafficking?

Accumulation of secondary events and progression to disease?

Brad S. Kahl, and David T. Yang Blood 2016;127:2055-2063
Follicular lymphoma-bone marrow biopsy - 1.

The arrow marks clusters of small lymphocytes (H&E). The paratrabecular distribution of involvement is a classic finding for follicular lymphoma.
Pathology of FL (2)

Follicular Lymphoma - 2.

Medium power showing back to back neoplastic follicles which have "lost" normal mantle zones.
According to WHO criteria, FL is morphologically graded into:
- grade 1 (<5 centroblasts per high-power field (hpf))
- grade 2 (6–15 centroblasts/hpf)
- grade 3 (>15 centroblasts/hpf)

Grade 3 is further subdivided into:
- grade 3A (centrocytes still present)
- grade 3B (the follicles consist almost entirely of centroblasts)

The WHO 2008 update now classifies grades 1 and 2 as low grade follicular lymphoma, grade 3A as high grade follicular lymphoma, and grade 3B as Diffuse Large B Cell Lymphoma (DLBCL).

Other factors to consider: Extranodal involvement:
- Bone marrow
- Peripheral Blood
- Spleen
- Liver

### Grading of FL

**Low Power (Architectural)**

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Loosely packed follicles</td>
<td>1. Tightly packed follicles</td>
</tr>
<tr>
<td>2. Polymorphic follicles</td>
<td>2. Monomorphic follicles</td>
</tr>
<tr>
<td>3. Prominent mantle zones</td>
<td>3. Absent or obscured mantle zones</td>
</tr>
<tr>
<td>4. Polarized follicles</td>
<td>4. Unpolarized follicles</td>
</tr>
<tr>
<td>5. Preserved open sinuses</td>
<td>5. Destroyed and constricted sinuses</td>
</tr>
<tr>
<td>6. No capsular invasion or transgression</td>
<td>6. Extension into perinodal soft tissue</td>
</tr>
<tr>
<td>7. Polyclonal light chain expression</td>
<td>7. Monoclonal light chain expression</td>
</tr>
</tbody>
</table>

**High Power (Cytological)**

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A very high mitotic rate</td>
<td>1. A lower mitotic rate</td>
</tr>
<tr>
<td>2. Tingible-body macrophages</td>
<td>2. No tingible-body macrophages</td>
</tr>
<tr>
<td>3. Between follicles are the usual paracortical lymphoid cells</td>
<td>3. Between follicles atypical cleaved cells may be found</td>
</tr>
</tbody>
</table>
Influence of the tumor microenvironment on FL

Follicular Dendritic Cell

Expression of:
Fc receptor
Mannose receptor
CD40 ligand

Secretion of:
IL-15
CXCL13

Follicular Helper T-cell

Expression of:
T-cell receptor
ICOS
CD40 ligand

Secretion of:
IL-4

Follicular Lymphoma

Expression of:
Fc receptor
Mannose receptor

Cytotoxic T-cell

Expression of:
T-cell receptor
FAS ligand

Secretion of:
TIA-1
Grenzyme B

Regulatory T-cell

Secretion of:
TGF-Beta
IL-10
Representative tissue microarray cores of follicular lymphoma stained for FOXP3

Prevalence of HIV infection in US lymphoma patients in the HAART era

179,520 patients with lymphoma from the US National Cancer Database, 2004-2009:

- Follicular lymphoma: 1.0%
- Peripheral T-cell lymphoma: 3.3%
- Hodgkin lymphoma: 4.7%
- Diffuse large B cell lymphoma: 5.4%
- Burkitt lymphoma: 29.0%
A model for the histogenesis of HIV-associated lymphomas showing molecular and viral pathogenesis and DLBCL taxonomy

<table>
<thead>
<tr>
<th>Germinal Center</th>
<th>Post-Germinal Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinal Center B-cell type (GCB)</td>
<td>Activated B-cell type (ABC)</td>
</tr>
<tr>
<td>Mild immunodeficiency</td>
<td>Severe immunodeficiency</td>
</tr>
<tr>
<td>Moderate CD4 count</td>
<td>Low CD4 count</td>
</tr>
<tr>
<td>Good Prognosis</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>Post-CART</td>
<td>Pre-CART</td>
</tr>
</tbody>
</table>

**Germinal Center B-cell type (GCB)**
- **BL**: CD20 +, EBV +/−, MUM1/IRF4 −, CD10/BCL6 +
- **DLBCL-CB**: CD20 +, EBV +/−, MUM1/IRF4 −, CD10/BCL6 +

**Post-Germinal Center**
- **DLBCL-IB**: CD20 +, EBV +/−, MUM1/IRF4 −, CD10/BCL6 +
- **PEL**: CD20 −, EBV +, KSHV/HHV8 +, MUM1/IRF4 −, CD10/BCL6 −
- **PB**: CD20 −, EBV +, KSHV/HHV8 +, MUM1/IRF4 −, CD10/BCL6 −

Kieron Dunleavy, and Wyndham H. Wilson *Blood* 2012;119:3245-3255
NCCN Guidelines Version 3.2017
Follicular Lymphoma (grade 1-2)

GELF CRITERIA\textsuperscript{a,b}

- 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\textsuperscript{a,c,d}

<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>

\textsuperscript{a}This provides useful prognostic information that may be used to guide therapeutic decisions.
\textsuperscript{e}The map is used to determine the number of nodal sites in FLIPI-1 criteria and is different than the conventional Ann Arbor site map.

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.

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An algorithmic approach to management of FL

Brad S. Kahl, and David T. Yang Blood 2016;127:2055-2063
**NCCN Guidelines Version 3.2017**  
Follicular Lymphoma (grade 1-2)

**SUGGESTED TREATMENT REGIMENS**  
(in preference order)

**First-line Therapy**
- Bendamustine + rituximab (category 1)
- Bendamustine + obinutuzumab\(^c\)
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- CHOP + obinutuzumab\(^c\)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- CVP + obinutuzumab\(^c\)
- Rituximab (375 mg/m\(^2\) weekly for 4 doses) (consider for low tumor burden)
- Lenalidomide + rituximab (category 2B)

**First-line Therapy for Elderly or Infirm** (If none of the above are expected to be tolerable in the opinion of treating physician)
- Rituximab (preferred) (375 mg/m\(^2\) weekly for 4 doses)
- Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab
- Radioimmunotherapy\(^e,f\) (category 2B)

**First-line Consolidation or Extended Dosing** (optional)
- Rituximab maintenance 375 mg/m\(^2\) one dose every 8 wks for 12 doses for patients initially presenting with high tumor burden (category 1)\(^g\)
- Obinutuzumab maintenance (1000 mg every 8 weeks for 12 doses)
- If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m\(^2\) one dose every 8 weeks for 4 doses
- Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)\(^e,f,h\) (category 2B)

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\(^a\)See references for regimens FOLL-B 3 of 4 and FOLL-B 4 of 4.

\(^b\)The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.

\(^c\)The clinical trial evaluating this regimen included obinutuzumab maintenance. The use without maintenance was an extrapolation of the data.

\(^d\)Rituximab may be appropriate in patients initially observed and with progression of low tumor burden disease not meeting GELF criteria (FOLL-A). Immediate initial therapy with rituximab in patients not meeting GELF criteria has not improved OS (Ardeshna K, et al. Lancet Oncol 2014;15:424-435).

\(^e\)Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for radioimmunotherapy.

\(^f\)If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Cytogenetics ± FISH for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT.

\(^g\)This is based on the PRIMA study for patients with high tumor burden treatment with RCVP and RCHOP. There are no data following other regimens.

\(^h\)The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.

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**Consider prophylaxis for tumor lysis syndrome** (See NHODG-B)  
See monoclonal antibody and viral reactivation (NHODG-B)

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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.
## BR vs R-CHOP Non-Heme Toxicities

<table>
<thead>
<tr>
<th></th>
<th>B-R (n=261)</th>
<th>R-CHOP (n=253)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>245 (100%)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>18 (7%)</td>
<td>73 (29%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>16 (6%)</td>
<td>47 (19%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Skin (erythema)</td>
<td>42 (16%)</td>
<td>23 (9%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Skin (allergic reaction)</td>
<td>40 (15%)</td>
<td>15 (6%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Infectious episodes</td>
<td>96 (37%)</td>
<td>127 (50%)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (&lt;1%)</td>
<td>8 (3%)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

B-R = bendamustine plus rituximab. R-CHOP = CHOP plus rituximab. *Includes only patients who received three or more cycles.

Histologic transformation of FL

• Histologic transformation: a biologic event leading to the development of a high-grade, aggressive non-Hodgkin lymphoma in patients with an underlying follicular lymphoma (FL).

• Transformation to diffuse large B-cell lymphoma (DLBCL) or Burkitt lymphoma is also known to take place in other subtypes of indolent lymphoma such as marginal zone lymphoma, lymphoplasmacytic lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia (Richter’s syndrome), and lymphocyte predominant Hodgkin lymphoma, but is best described as occurring in FL.

• Survival after transformation has historically been poor, but has improved in the rituximab era.
Mutational analyses of FL clonal architecture yields insights into histologic transformation
Risk of transformation curve based on FOXP3 immunoarchitectural patterns

Follicular (n=38)

Diffuse (n=64)

$P = .002$

Overall survival curve based on FOXP3 immunoarchitectural patterns


©2010 by American Society of Hematology
Approach to treatment of transformed FL

Clinical Suspicion of HT

FDG PET Scan

Biopsy Site with High SUV

Confirm HT

Older Patient Comorbidities

Lenalidomide

RCHOP X 6

Consider Radioimmunotherapy Consolidation

Young Fit Patient

Anthracycline Naïve?

No

Salvage Chemo + HDT/ASCT

Yes

RCHOP X 6

Consider HDT/ASCT

Figure 2. Approach to treatment of transformed FL.
Post transformation survival for confirmed and suspected histologic transformation of FL

Survival curves of HIV+ individuals with lymphoma

Figure 1.

Han et al., Cancer Epidemiol Biomarkers Prev March 1 2017 (26) (3) 303-311; DOI: 10.1158/1055-9965.EPI-16-0595
References

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- http://pleiad.umdnj.edu/hemepath/follicular/follicular.html