Lymphoma Tumor Board

Treatment and Management of Indolent Non-Hodgkin Lymphoma

March 31, 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: 2%
- 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 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)

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)

- 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)

Primary CNS Lymphoma (See NCCN Guidelines for CNS)
Waldenström’s Macroglobulinemia/Lymphoplasmacytic Lymphoma (See NCCN Guidelines for WM/LPL)
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
- 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}\n
t(14;18) – Cytogenetic hallmark of FL
Model of FL pathogenesis
Pathology of FL (1)

Follicular lymphoma-bone marrow biopsy - 1.

Image ID: 1029

Authors: Peter Maslak

The arrow marks clusters of small lymphocytes (H&E). The paratrabecular distribution of involvement is a classic finding for follicular lymphoma.
Medium power showing back to back neoplastic follicles which have "lost" normal mantle zones.
Grading of FL

- According to the 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
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
- Secretion of: TIA-1, Granzyme B

Regulatory T-cell
- Secretion of: TGF-Beta, IL-10

Expression and secretion of various proteins and receptors related to the interaction between different cell types in the tumor microenvironment.
NCCN Guidelines Version 3.2017
Follicular Lymphoma (grade 1-2)

GELF CRITERIA\(^a, b\)

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

FLIPI - 1 CRITERIA\(^a, c, d\)

| Age | \(\geq 60\) y |
| Ann Arbor stage | III–IV |
| Hemoglobin level | <12 g/dL |
| Serum LDH level | >ULN (upper limit of normal) |
| Number of nodal sites\(^d\) | \(\geq 5\) |

Risk group according to FLIPI chart

<table>
<thead>
<tr>
<th>Number of factors</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–1</td>
<td>2</td>
<td>(\geq 3)</td>
</tr>
</tbody>
</table>

\(^a\)This provides useful prognostic information that may be used to guide therapeutic decisions.


\(^e\)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.
An algorithmic approach to management of FL

A

Advanced stage, newly diagnosed grade 1–2 or 3a follicular lymphoma

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low tumor burden</td>
<td>Low tumor burden</td>
</tr>
<tr>
<td>High tumor burden</td>
<td>High tumor burden</td>
</tr>
</tbody>
</table>

Watch/wait vs Single-agent rituximab

Watch and wait can be considered in select patients

Consider patient age and comorbidities when selecting chemo backbone

B

Relapsed follicular lymphoma

Rapidly growing nodes, elevated LDH, extranodal involvement

Yes

No

Biopsy

Low tumor burden

Consider watch & wait

High tumor burden

Prior R-chemo?

FL

Transformed

R-chemo ± high-dose therapy and AutoSCT

Yes

No

R-chemo ± maintenance R

Remission length ≤ 2 yrs

Remission length > 2 yrs

Consider clinical trial of novel agents

Consider AutoSCT if in 1st remission & transplant eligible

Consider additional R-chemo or targeted agents

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

SUGGESTED TREATMENT REGIMENSa,b
(in preference order)

First-line Therapy
- Bendamustine + rituximab (category 1)
- Bendamustine + obinutuzumabc
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- CHOPl + obinutuzumabc
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- CVP + obinutuzumabc
- Rituximab (375 mg/m² weekly for 4 doses) (consider for low tumor burden)d
- 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/m² weekly for 4 doses)
- Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab
- Radioimmunotherapye,f (category 2B)

First-line Consolidation or Extended Dosing (optional)
- Rituximab maintenance 375 mg/m² 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/m² one dose every 8 weeks for 4 doses
- Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)e,f,h (category 2B)

See Second-line and Subsequent Therapy on FOLL-B 2 of 4

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

aSee references for regimens FOLL-B 3 of 4 and FOLL-B 4 of 4.
bThe 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.
cThe clinical trial evaluating this regimen included obinutuzumab maintenance. The use without maintenance was an extrapolation of the data.
dRituximab 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 2014:15:424-436).
eSelection 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.

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## BR vs R-CHOP Non-Heme Toxicities

<table>
<thead>
<tr>
<th>Toxicity</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>

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

Histologic transformation of 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.
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?
          - Yes
            - RCHOP X 6
          - No
            - Salvage Chemo + HDT/ASCT
              - Consider HDT/ASCT

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

Marginal Zone Lymphoma - 1.

Image ID: 2854
Authors: Marshall Kadin

Category: Lymphoma: Mature B-cell neoplasms > Low-grade B-cell lymphoma > Nodal Marginal Zone Lymphoma
Marginal Zone Lymphoma - 2.

Image ID: 2855
Authors: Marshall Kadin

Category: Lymphoma: Mature B-cell neoplasms > Low-grade B-cell lymphoma > Nodal Marginal Zone Lymphoma
Splenic Marginal Zone Lymphoma With Villous Lymphocytes – Peripheral Blood - 3.

Image ID: 3299
Authors: Peter Maslak

Category: Lymphoma: Mature B-cell neoplasms > Splenic lymphomas > Splenic Marginal Zone Lymphoma
Splenic Marginal Zone Lymphoma With Villous Lymphocytes – Peripheral Blood - 6.

Image ID: 3302
Authors: Peter Maslak

Category: Lymphoma: Mature B-cell neoplasms > Splenic lymphomas > Splenic Marginal Zone Lymphoma
Gastric MALT Lymphoma - 1.

Image ID: 2071
Authors: Marshall Kadin

Category: Lymphoma: Mature B-cell neoplasms > Low-grade B-cell lymphoma > Extranodal Marginal Zone Lymphoma
Gastric MALT Lymphoma - 2.

Image ID: 2072
Authors: Marshall Kadin

Category: Lymphoma: Mature B-cell neoplasms > Low-grade B-cell lymphoma > Extranodal Marginal Zone Lymphoma
Gastric MALT Lymphoma - 3.

Image ID: 2073
Authors: Marshall Kadin

Category: Lymphoma: Mature B-cell neoplasms > Low-grade B-cell lymphoma > Follicular Lymphoma
Gastric MALT Lymphoma - 1.

Image ID: 2191
Authors: Marshall Kadin

Category: Lymphoma: Mature B-cell neoplasms > Low-grade B-cell lymphoma > Extranodal Marginal Zone Lymphoma
Treatment algorithm for the management of gastric MALT lymphoma confined to the stomach, with or without regional lymph node involvement

Emanuele Zucca, and Francesco Bertoni Blood 2016;127:2082-2092
MALT Lymphoma, Lung - 1.

Image ID: 2182
Authors: Marshall Kadin

Category: Lymphoma: Mature B-cell neoplasms > Low-grade B-cell lymphoma > Extranodal Marginal Zone Lymphoma
MALT Lymphoma, Lung - 2.

Image ID: 2183
Authors: Marshall Kadin

Category: Lymphoma: Mature B-cell neoplasms > Low-grade B-cell lymphoma > Extranodal Marginal Zone Lymphoma
Histological features of primary cutaneous B-cell lymphomas. (a) Primary cutaneous marginal zone B-cell lymphomas is an indolent lymphoma composed of small B cells, including marginal zone (centrocyte-like), lymphoplasmacytoid and plasma cells. Immunohistologically, the neoplastic cells express CD20, CD79a and Bcl-2, and are negative BCL-6. (b) PCFCL is a tumor of neoplastic follicle center cells, with a mixture of centrocytes and centroblasts. Different growth patterns can be found, including purely follicular, mixed follicular and diffuse patterns, and a diffuse growth pattern. The neoplastic follicle center cells express CD20, CD79a and Bcl-6. PCFCL does not commonly expresses BCL-2.
Pathology - Waldenstrom’s macroglobulinemia

[Waldenstrom’s macroglobulinemia (WM)]. This clonal bone marrow disorder is morphologically characterized by a neoplastic proliferation of small lymphocytes, plasma cells, and plasmacytoid lymphocytes. Involvement of lymph node, spleen and other lymphoid tissue takes the form of lymphoplasmacytic lymphoma (LPL). Isolated involvement by LPL without bone marrow involvement may not produce the characteristic clinical syndrome. The bone marrow involvement ranges from mild to diffuse but is involved in all cases with the typical clinical syndrome.
References


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• http://www.pathpedia.com/education/eatlas/histopathology/bone_marrow/waldenstrom_macroglobulinemia.aspx
• https://en.wikipedia.org/wiki/Follicular_lymphoma
• https://lymphomanewstoday.com/2017/01/10/follicular-lymphoma-can-develop-along-two-paths/
• https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#b-cell
• http://pleiad.umdnj.edu/hemepath/follicular/follicular.html