Non-Hodgkin Lymphoma – Know Your Subtype

James Armitage, MD
The Joe Shapiro Professor of Medicine
Division of Oncology/Hematology
University of Nebraska Medical Center
Lincoln, NE

Wednesday, May 24, 2017
NHL Types

MATURE B-CELL NEOPLASMS
- Chronic lymphocytic leukaemia / small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Hairy cell leukaemia
- Splenic B-cell lymphoma / leukaemia, unclassifiable
- Splenic diffuse red pulp small B-cell lymphoma
- Hairy cell leukaemia-variant
- Lymphoplasmacytic lymphoma
- Extramedullary marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- Pediatric nodal marginal zone lymphoma
- Follicular lymphoma
- In situ follicular neoplasia
- Pediatric type follicular lymphoma
- Large B-cell lymphoma with IRF4 rearrangement
- Primary cutaneous follicle centre lymphoma
- Mantle cell lymphoma
- In situ mantle cell neoplasia
- Diffuse large B-cell lymphoma (DLBCL), NOS
- T cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL, not otherwise specified
- EBV+ Mucocutaneous ulcer
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV8 positive DLBCL, NOS
- Burkitt lymphoma
- Burkitt-like lymphoma with 11q aberrations
- High grade B-cell lymphoma, with BCL2 and/or BCL6 and MYC rearrangements
- High grade B-cell lymphoma, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
MATURE T-AND NK-NEOPLASMS

- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- Chronic lymphoproliferative disorder of NK cells
- Aggressive NK cell leukaemia
- Epstein-Barr virus (EBV) positive T-cell lymphoproliferative diseases of childhood
- Chronic Active EBV infection, Cutaneous
- Hydroa vacciniforme-like lymphoma
- Severe mosquito bite hypersensitivity
- Chronic Active EBV infection, Systemic
- Systemic EBV+ T-cell Lymphoma of childhood
- Adult T-cell leukaemia/lymphoma
- Extramedullary NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Indolent T-cell lymphoproliferative disorder of the GI tract
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides

Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous acral CD8+ T-cell lymphoma
- Primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Anaplastic large cell lymphoma, ALK positive
- Anaplastic large cell lymphoma, ALK negative
- Breast implant-associated anaplastic large cell lymphoma
Frequency of REAL Classification NHL Subtypes

N = 1,403

REAL = Revised European American Lymphoma; NHL = non-Hodgkin lymphoma; FL = follicular lymphoma; DLBCL = diffuse large B-cell lymphoma.


Diffuse Large B-cell Lymphoma
As We Learn More About the Biology of Lymphomas, it is Clear That Diffuse Large B-Cell Lymphoma is Not Just One Disease

Subtypes of Diffuse Large B-Cell Lymphoma In The 2008 WHO Classification

<table>
<thead>
<tr>
<th>Morphological</th>
<th>Genetic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centroblastic</td>
<td>GCB</td>
<td>EBV positive in elderly</td>
</tr>
<tr>
<td>Immunoblastic</td>
<td>Non GCB (includes ABC)</td>
<td>With chronic inflammation</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>Double hit</td>
<td>In lymphomatoid granulomatous</td>
</tr>
<tr>
<td>Plasmablastic</td>
<td>By Primary Site</td>
<td>In HHV-8 associated</td>
</tr>
<tr>
<td></td>
<td>CNS</td>
<td>Castlemans</td>
</tr>
<tr>
<td>Immunological</td>
<td>Cutaneous leg type</td>
<td>Interface lymphomas</td>
</tr>
<tr>
<td>ALK positive</td>
<td>Mediastinal</td>
<td>DLBCL/Burkitt</td>
</tr>
<tr>
<td>CD5 positive</td>
<td>Intravascular Effusion</td>
<td>NSHD/DLBCL</td>
</tr>
</tbody>
</table>


It is Possible That Some “Subtypes” Might Benefit From Specific Treatments

Conclusion

• Diffuse large B-cell lymphoma is not just one disease
• There is not one “best” regimen for all patients, although CHOP-R remains the “standard”
• New drugs and a better understanding of molecular subtypes will almost certainly change the therapy for these patients
Follicular Lymphoma

Follicular Lymphoma is a Much More Complex Disorder Than is Sometimes Recognized
Can Follicular Lymphoma Be Accurately Sub-typed (Graded)?

<table>
<thead>
<tr>
<th>Type</th>
<th>Accuracy of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular Small Cleaved (Grade 1)</td>
<td>72%</td>
</tr>
<tr>
<td>Follicular Mixed (Grade 2)</td>
<td>61%</td>
</tr>
<tr>
<td>Follicular Large Cell (Grade 3)</td>
<td>60%</td>
</tr>
</tbody>
</table>

What About Distinguishing FL 3A vs. FL 3B??
Should Follicular Lymphoma Grade 3 Be Treated Differently?

Is Survival Improving for Low Grade Follicular Lymphoma?
Patients With Low Grade Follicular Lymphoma Treated in the NLSG

Mantle Cell Lymphoma
**Mantle Cell Lymphoma History**

- 1974, lymphocytic lymphoma of intermediate differentiation (Berard, et al)
- 1974, centrocytic lymphoma (Lennert, et al)
- 1982, mantle zone lymphoma (Weisenburger, Rappaport)
- 1987, association of intermediate lymphocytic lymphoma with t(11;14)
- 1990, association of intermediate lymphocytic lymphoma with Bcl-1 (cyclin-D1)
- 1992, mantle cell lymphoma

**Overall Survival Small Round Cell Tumors**

![Graph showing survival rates over years for different types of small round cell tumors.](image)

Log Rank Test p<0.001

*JCO 1998; 16: 2780*
Mantle Cell Histological Appearance

- Diffuse
- Nodular
- Blastic
Mantle Cell Lymphoma Presenting as “CLL”

- Often splenomegaly without lymphadenopathy
- Frequently asymptomatic
- Reported median survival ~6 years
- Some patients go >5 years without therapy

Blood 2003; 101:4975

Conclusion

The survival of patients with mantle cell lymphoma has improved considerably with better understanding of the disease, the advent of rituximab, and clinical trials studying comparative effectiveness of available regimens. Several active new agents make it likely that the outcome will continue to improve.
Marginal Zone Lymphoma

Marginal Zone Lymphomas as a Percent of All Non-Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>Type</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALT</td>
<td>7.6%</td>
</tr>
<tr>
<td>Nodal</td>
<td>1.8%</td>
</tr>
<tr>
<td>Splenic</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
Overall Survival Small Round Cell Tumors

Log Rank Test p<0.001

MALT Lymphoma
An Antigen-dependent Process
Features suggesting an antigen-driven growth of MALT Lymphoma

- Histologic features
  - Reactive lymphoid follicles and follicular colonization
  - Scattered transformed cells in cell cycle
  - Plasma cell differentiation
  - Large amount of intratumoral T-cells
- Association with chronic infectious and acute-immune processes
- Mutation pattern of immunoglobulin gene
- Therapeutic efficacy of antibiotics
Small Lymphocytic/Chronic Lymphocytic Leukemia

Virchow: Initial Description CLL
The Names Can Sometimes Be Confusing

• CLL
• SLL
• Monoclonal B lymphocytosis

All typically Have CD5+, CD10-, CD20 dim, CD23+ Small Lymphocytes

Differential Diagnosis

• Lymphoplasmacytic lymphoma
• Hairy cell leukemia
• MALT lymphoma
• Nodal marginal zone lymphoma
• Splenic marginal zone lymphoma
• B-cell prolymphocytic leukemia
• Mantle cell lymphoma
• Follicular lymphoma
Peripheral T-Cell Lymphoma

Indolent PTCLs

- Mycosis fungoides
- Chronic, smoldering ATL
- CD30+, primary cutaneous lymphoproliferative disorders
Spectrum of CD30+ Cutaneous Lymphoproliferative Disorders

- Lymphomatoid papulosis (ALK-)
- Primary cutaneous ALCL (usually ALK-)
- Systemic ALCL with skin involvement (ALK+/-)
- All CD30+ and rearranged TCR genes

Aggressive PTCLs
Anaplastic Large Cell Lymphoma

• Previously confused with other malignancies
• B-cell variant exists
• Sub-divided by ALK expression

ALCL and Breast Implants
NK/T Cell Lymphomas

Nasal vs Nasal-type

Hepatosplenic Gamma/Delta T-cell Lymphoma

- Difficult to diagnose
- Liver, spleen and marrow infiltrated
- Sinusoidal pattern – not tumors
- Poor prognosis
Enteropathy-Type Intestinal T-cell Lymphoma

- Often gluten-sensitive enteropathy (32% in International Study)
- Treating celiac disease seems to prevent lymphoma
- Poor prognosis

Burkitt Lymphoma
Burkitt Lymphoma Was the First Malignancy to Be Cured With Chemotherapy

Treatment Outcome for Adult Burkitt Lymphoma Using Dose-Intensive Regimens

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Regimen</th>
<th>EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI</td>
<td>Magrath</td>
<td>92%</td>
</tr>
<tr>
<td>NCI</td>
<td>Magrath</td>
<td>84%</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>R-HyperCVAD</td>
<td>80%</td>
</tr>
<tr>
<td>NCI</td>
<td>R-EPOCH</td>
<td>93%</td>
</tr>
</tbody>
</table>
In Burkitt Lymphoma it is a Tragedy to:

1. Misdiagnose
2. Delay treatment
3. Not give correct doses of an intensive regimen on schedule
Q&A Session

Ask a question by phone:
• Press star (*) then the number 1 on your keypad.

Ask a question by web:
• Click “Ask a question”
• Type your question
• Click “Submit”

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

SUPPORT RESOURCES
• Online Chats: Online moderated chat forums: www.LLS.org/chat
• Questions to ask your treatment team: www.LLS.org/whattoknow
• Free education materials: www.LLS.org/booklets
• Past NHL education programs: www.LLS.org/programs
• Additional information on NHL: www.LLS.org/NHL
• Information Resource Center: Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  ➢ EMAIL: infocenter@LLS.org
  ➢ TOLL-FREE PHONE: (800) 955-4572