Grand Rounds: Update in Non-Hodgkin’s Lymphoma

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Disclosure

- Dr. Vose has received research grant support from the following:
  - Allos Therapeutics/Spectrum
  - Bristol-Myers Squibb
  - Celgene
  - Genentech
  - GlaxoSmithKline
  - Incyte Corp.
  - Janssen Biotech
  - Pharmacyclics
  - US Biotech, Inc.

- Ms. Byar has nothing to disclose.

Learning Objectives

- Describe current treatment and medical progress for patients with advanced non-Hodgkin’s lymphoma (NHL)
- List optimal imaging approaches in the patient newly diagnosed with NHL
- Summarize the role of genomics in therapeutic treatment of NHL
- Utilize strategies for the management of treatment-related toxicities in patients with NHL, within the context of a multidisciplinary team
Non-Hodgkin’s Lymphoma

- Heterogeneous group of neoplasms with differing patterns of growth and response to treatment
- New cases
  - Estimated 70,800 new cases in 2014
  - NHL ranks 6th among men and 5th among women as the most frequently newly diagnosed cancer
- Deaths
  - NHL will account for an estimated 18,990 deaths in 2014 (approximately 3% of all cancer deaths)
  - NHL is the 9th leading cause of cancer death in men and the 7th leading cause of cancer deaths in women

Signs and Symptoms

- Signs
  - Lymphadenopathy
    - Often asymptomatic
  - Fatigue
  - Cough, SOB
  - Abdominal pain, early satiety
  - B symptoms
    - Fever
    - Weight loss
    - Night sweats
- Advanced disease
  - Fatigue
  - Anemia
  - Tumor lysis
  - Hydronephrosis
  - Bowel obstruction
  - Superior vena cava syndrome
  - Pleural effusions

SOB = shortness of breath


Diagnostic Workup

- Thorough physical examinations and evaluation of performance status and constitutional symptoms
  - Laboratory:
    - CBC with differential, LDH, comprehensive metabolic panel, hepatitis B, HCG, HCV, HIV, serum β2 microglobulin, uric acid
    - Bone marrow aspirate and biopsy
    - MUGA scan/echocardiogram
    - CT or PET-CT
    - Site specific

CBC = complete blood count; LDH = lactate dehydrogenase; HCG = human chorionic gonadotropin; CT = computed tomography; MUGA = multigated acquisition scan; ECHO = echocardiogram


What is the minimum wait after the previous chemotherapy administration before scanning the patient for an interim assessment PET-CT?

A. 1 month JL220
B. 3 weeks JL221
C. 6 weeks JL222
D. 3 months JL223

The Role of PET-CT

- Used for staging and interim response to treatment
- Focal FDG uptake within bone or BM, liver, and spleen is highly suggestive for involvement of HL and aggressive NHL and may obviate the need for BM biopsy
- PET-CT can miss low-volume BM involvement of < 20% and co-existent low-grade lymphoma in DLBCL
- Scan minimum of 3 weeks after administration of chemotherapy but preferably 6-8 weeks after completion of last cycle
- 3 months after last RT is recommended
- End-of-treatment remission assessment is more accurate with PET-CT then CT alone for patients with HL, DLBCL, and higher-burden FL
- CT is indicated for non-avid histologies
  - CLL/SLL, MZL, MF

BM = bone marrow; HL = Hodgkin's lymphoma; DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; MZL = marginal zone lymphoma; MF = myelofibrosis

Deauville Scale

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum ≤ liver
4. Uptake moderately higher than liver
5. Uptake markedly higher than liver and/or new lesions
X. New areas of uptake unlikely to be related to lymphoma

Lymphoma Staging
Ann Arbor Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Single lymph node region</td>
</tr>
<tr>
<td>II</td>
<td>2 or more node regions, same side as diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Node regions, both sides of diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse extranodal lymphatic involvement</td>
</tr>
</tbody>
</table>

For all stages:
A. No symptoms
B. Weight loss >10% over 6 months, fever (38°C), drenching night sweats

For stages I–III:
E. Involvement of a single extranodal site contiguous or proximal to known node site

Revised Response Criteria for NHL
(Including PET)

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
<th>System, Linear</th>
<th>BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Regression of measurable disease and no new sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR or PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>Relapsed disease or PD</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; BM = bone marrow; SPD = sum of product of diameters; FDG = fludeoxyglucose; PET = positron emission tomography; NCCN = National Comprehensive Cancer Network; NHL = non-Hodgkin’s lymphoma.
Revised Criteria for Response Assessment Based on PET-CT Response

<table>
<thead>
<tr>
<th>Nodes and extralymphatic sites</th>
<th>Complete metabolic response (CMR)</th>
<th>Partial metabolic response</th>
<th>No metabolic response</th>
<th>Progressive metabolic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 1: 1-2 with or without residual mass</td>
<td>Site 1: 3.5 reduced from baseline with none of any size</td>
<td>Site 2: 4.5 reduced from baseline with none of any size</td>
<td>Site 3: 4 with no change from baseline</td>
<td>Site 4: 4 increased over baseline New FDG-avid lesion</td>
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Follicular Lymphoma

- More common in older patients
- Many with preexisting conditions
- Indolent course
- Waxing and waning progression
- Advanced stage at diagnosis
- Shorter remissions between treatments
- Median survival: 10-15 years - incurable
- Transformation to diffuse large B-cell NHL common

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Follicular Lymphoma: Grades 1–3

Cytogenetics demonstrates t(14;18) in 90% Molecular analysis: bcl-6 positive and bcl-2 positive in 70%–95%

<table>
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<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly small cells (centrocytes predominate) few centroblasts present</td>
<td>Mixture of small and large cells (both centrocytes and centroblasts present) approximately 2–15/Hpf</td>
<td>Predominantly large cells</td>
</tr>
<tr>
<td>85%–95% of FL</td>
<td>35% of FL</td>
<td>20% of FL</td>
</tr>
<tr>
<td>Indolent</td>
<td>Indolent</td>
<td>Clinically aggressive</td>
</tr>
<tr>
<td>Generally incurable</td>
<td>Generally incurable</td>
<td>May be curable</td>
</tr>
</tbody>
</table>

- Two subtypes: FL3A—composed of centroblasts and centrocytes (>15/Hpf), FL3B—mainly centroblasts; often does not have t(14;18)/BCL2 rearrangement but has a BCL-6 rearrangement that is more closely like a DLBCL.


Follicular Lymphoma
International Prognostic Index

Risk factors: 1 pt each
- Age > 60 years
- LDH > ULN
- Hgb < 12 g/dL
- Ann Arbor stage III–IV
- > 4 involved nodal sites

LDH = lactate dehydrogenase; ULN = upper limit of normal.


Watchful Waiting vs. Immediate Treatment in Indolent Lymphoma

Observation (n=151) vs. Chemotherapy (n=158)
Indications for Therapy in Follicular Lymphoma

- Progressive local disease or change in tempo
- Systemic or constitutional symptoms
- Cytopenias due to marrow involvement
- High tumor burden
- Leukemic phase
- Organ invasion
- High-risk disease based on FLIPI score
- Transformation

FLIPI = Follicular Lymphoma International Prognostic Index

Revalidation of FLIPI in Patients With Follicular Lymphoma Treated With R-Chemo: PFS by FLIPI (Cox Stratified by Rituximab)

3-y PFS

PFS = progression-free survival

GELA PRIMA Phase III Study: Rituximab Maintenance in Follicular Lymphoma

Primary endpoint: PFS
Secondary endpoints: EFS, OS

EFS = event-free survival; OS = overall survival
Friedberg JW. Lancet. 2011;377:4-6
Primary Endpoint (PFS) Met at the Planned Interim Analysis

Rituximab maintenance significantly reduced the risk of progression by 50%, but OS the same

Stratified HR = 0.50
95% CI 0.39; 0.64
p < .0001

Time (months)

Patients at risk

Rituximab maintenance
N = 505
Observation
N = 513

62%
46%
30%
14%
0

Progression rate

[Graph showing progression rate over time]

HR = hazard ratio; CI = confidence interval.

Friedberg JW. Lancet. 2011;377:4-6

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Follicular Lymphoma (grades 1-2)

SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

First-line Therapy
- Bendamustine + rituximab (category 1)
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- Rituximab (375 mg/m² weekly for 4 doses)

First-line Therapy for Elderly or Infirn (if none of the above are expected to be tolerable in the opinion of treating physician)
- Rituximab
- Rituximab (preferred) (375 mg/m² weekly for 4 doses)
- Single-agent alkylators (e.g., chlorambucil or cyclophosphamide) + rituximab

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)
- If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m² one dose every 8 weeks for 4 doses.

Second-line and Subsequent Therapy
- Chemotherapy (as listed under first-line therapy)
- FCRR (fludarabine, cyclophosphamide, rituximab) (category 1)
- Fludarabine + rituximab
- Lenalidomide + rituximab
- Rituximab
- RFID (rituximab, fludarabine, mitoxantrone, dexamethasone)
- See Second-line Therapy for DLBCL (BCEI ≤ 1 of 3) without regard to transplantability

Second-line Consolidation or Extended Dosing
- High dose therapy with autologous stem cell rescue
- Allogeneic stem cell transplant for highly selected patients
- Rituximab maintenance (category 1) 375 mg/m² one dose every 12 weeks for 2 years (category 1) (optional)

For patients with locally bulky or symptomatic disease, consider IFRT 4-30 Gy ± additional systemic therapy.
Histologic Transformation From a Follicular Lymphoma

- Risk of transformation is approximately 3% per yr
- Risk factors for transformation
  - Advanced stage at diagnosis
  - Elevated LDH
  - β2-microglobulin level > 3 mg/L
  - Low serum albumin
  - Histologic grade 3
  - High FLIPI score
  - Lack of CR following initial therapy
- Transformation from FL to DLBCL has a poorer overall survival than de novo DLBCL

The Incidence of Transformed Lymphoma

Lyon: n = 220
St. Barts: n = 325
Vancouver: n=600
Transformation rate ~ 30% at 10 years

The Outcome for Patients With TL

Median survivals range from 1 to 2 years

Lyon
St. Barts
Vancouver
Diffuse Large B-Cell Lymphoma

- Most common sub-type of NHL
  - 31% of all cases
- More common with advanced age
  - 54% of NHL cases in patients > 65 years
- Majority of patients have advanced disease at the time of diagnosis
  - Stage III or stage IV
- Chemotherapy + rituximab is the primary treatment approach in this disease

**International Prognostic Index**

<table>
<thead>
<tr>
<th>Criteria (&quot;APLES&quot;)</th>
<th>Risk group</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≤ 60 vs. &gt; 60 years)</td>
<td>Low</td>
<td>0-1</td>
</tr>
<tr>
<td>Performance status (0 or 1 vs. ≥ 2)</td>
<td>Low-intermediate</td>
<td>2</td>
</tr>
<tr>
<td>LDH (≤ 1 vs &gt; 1 times normal)</td>
<td>High-intermediate</td>
<td>3</td>
</tr>
<tr>
<td>Extranodal sites (≤ 1 vs. &gt; 1)</td>
<td>High</td>
<td>4-5</td>
</tr>
<tr>
<td>Stage (I or II vs. III or IV)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age-adjusted criteria (patients ≤ 60 years)
| Performance status (0 or 1 vs. ≥ 2) | Low | 0 |
| LDH (≤ 1 vs > 1 times normal) | Low-intermediate | 1 |
| Stage (I or II vs. III or IV) | High-intermediate | 2 |
| | High | 3 |
**NCNN Guidelines Version 3.2014**

**Diffuse Large B-Cell Lymphoma**

**SUGGESTED TREATMENT REGIMENS**

(in alphabetical order)

**First-line Therapy**
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- Dose-dense RCHOP 14 (category 3)
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (category 2B)

**First-line Therapy for patients with poor left ventricular function**
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RHCO (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- RCHOP (rituximab, cyclophosphamide, mitoxantrone, vincristine, prednisone)
- DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
- RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)

**First-line Consolidation (optional)**
- High dose therapy with autologous stem cell rescue in patients with age-adjusted IPI high-risk disease (category 2B)

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**SWOG, ECOG, CALGB, NCIC – S9704**

Early vs. Delayed High-Dose Therapy in High Intermediate/High IPI DLBCL

**CHOP – R x 5**

Evaluate for Response

Less Than Partial Response

ICE Salvage

Complete or Partial Response

(Enter Randomization)

CHOP – R x 1

Evaluate

Responders to ASCT

Complete or Partial Response

(Enter Randomization)

CHOP – R x 3

ASCT

Cure

Relapse

Mobilization

ICE Preferred

ASCT

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**Outcome of All Randomized Patients Based on IPI:**

PFS/OS

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**Stiff PJ, et al.**

*J Clin Oncol.* 2011;29;abstract 8001

---

**Stiff PJ, et al.**

*J Clin Oncol.* 2011;29;abstract 8001
CALGB 50303: R-CHOP vs R-EPOCH in Newly Diagnosed DLBCL

- R-CHOP every 3 wks for 6 cycles
- R-EPOCH
  - Doxorubicin, etoposide, vincristine Days 1-4
  - cyclophosphamide Day 5
  - prednisone Days 1-5

- Primary endpoints: EFS, molecular predictors of outcome for each regimen
- Secondary endpoints: RR, OS, toxicity, use of molecular profiling for pathologic diagnosis

Untreated patients with newly diagnosed DLBCL (N = 478)

Which type of genetic profiling group of DLBCL has a poorer prognosis?

A. Activated B-cell type (ABC) JL224
B. Germinal center B-cell (GCB) JL225
C. Primary mediastinal B-cell (PBML) JL226
D. None of the above; they are all the same JL227

Survival Rates in Different DLBCL Genetic Groups

- Activated B-cell–like diffuse large B-cell lymphoma (ABC)
- Germinal center B-cell–like (GCB)
- Primary mediastinal B-cell lymphoma (PBML)

Survival Rates

<table>
<thead>
<tr>
<th>Genetic Group</th>
<th>5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>30%</td>
</tr>
<tr>
<td>GCB</td>
<td>59%</td>
</tr>
<tr>
<td>PMBL</td>
<td>64%</td>
</tr>
</tbody>
</table>

Which are typical molecular markers seen with a “double-hit” lymphoma?

A. BCL-6 and c-myc+  JL228
B. BCL-6 and BCL-2  JL229
C. BCL-2 and c-myc+  JL230
D. None of the above  JL231
What about other specific subtypes defined pathologically/molecularly?

- B-cell lymphoma intermediate between DLBCL and BL (Grey zone)
- B-cell lymphoma intermediate between DLBCL and Hodgkin lymphoma
- C-MYC+
- “Double hit” (bcl-2 and c-myc+ by FISH)
- “Triple hit” (bcl-2, bcl-6, and c-myc+ by FISH)

Impact of “double protein” IHC on survival

Coral Trial of R-ICE vs. R-DHAP

Which salvage regimen is the best?

Place of immunotherapy posttransplantation?

Early Relapse and Prior Rituximab Defines a High-Risk Population

By ITT analysis (includes many patients who never underwent ASCT): 52% of randomized patients were transplanted.

Rituximab has failed to prevent relapses?
How many patients will be eligible for salvage post-ASCT?
CORAL Maintenance: EFS according to treatment arm (MITT)
Mantle Cell Lymphoma

Mantle cell lymphoma with area of remnant nodal architecture

Mantle Cell Lymphoma

- B-cell origin
- Median age: 63 yr at diagnosis
- Indolent morphology
- Aggressive clinical course
  - Typically stage III-IV at diagnosis
  - Extramedullary involvement common (BM, spleen, GI)
  - t(11;14)(q13;q32) translocation / bcl-1 gene
    - ↑ cyclin D1 expression
    - ↑ cell cycle progression
- Poor prognosis / Incurable
  - Median PFS: ~ 2-3 years after initial treatment
  - Median OS: ~ 3-5 years

4 independent prognostic factors for survival (age, PS, LDH, leukocyte counts)
- LR: 0–3 points
- IR: 4–5 points
- HR: 6–11 points

Ann Arbor stage, BM involvement, number of extranodal sites used in the IPI were not prognostically relevant in MCL

More recent studies have added the proliferation index (Ki-67 > 30)

Mantle Cell Lymphoma IPI (MIPI)

- PS = performance score, LDH = lactate dehydrogenase, Ki-67 = high rate
- LR: Median not reached
- IR: Median 51
- HR: Median 29

OS According to MIPI

PB = performance score; LDH = lactate dehydrogenase; Ki-67 = high rate
Antigen-Dependent B-Cell Receptor (BCR) Signaling and its Targeting by Small-Molecule Inhibitors

Managing Treatment-Related Toxicities

Is a Multidisciplinary Approach
Multidisciplinary Approach to the Care of NHL Patients

- Collaborate with all members of the multidisciplinary team in an effort to provide a high-quality comprehensive cancer service for people with cancer and their families
- Advanced practitioner (AP) plays a major role in working with the team coordinating care and ensuring that patients and caregivers receive all the resources that they need throughout the trajectory of their cancer care and management of treatment-related toxicities
- Evidence-based decision-making in managing treatment-related toxicities is crucial and an agreed collaborative agreement between the AP and provider should be established
- Establish a comprehensive plan of care as patients transition from active treatment to survivorship or end-of-life care
- Communication is KEY

Key Takeaways

- PET-CT standard for FDG-avid lymphomas and in some cases may even obviate the need for BM biopsy
- Scan minimum of 3 weeks after administration of chemotherapy but preferably 6-8 weeks after completion of last cycle
- 3 months after last RT is recommended
- End of treatment remission assessment is more accurate with PET-CT then CT alone for patients with HL, DLBCL, and higher-burden FL
- CT imaging is indicated for non-avid histologies
  - CLL/SLL, MZL, MF

Key Takeaways

- Rituximab maintenance significantly reduced the risk of progression by 50%, but OS is the same
- Understanding the specific cytogenetic and molecular abnormalities of the individual subtypes of lymphoma can assist in treatment decision making
- Managing toxicities requires a multidisciplinary approach among APs and other healthcare providers
- Ongoing communication is key in managing patients with NHL
- Surveillance scans following remission are discouraged, especially for DLBCL