Lymphoma Overview and Report Forms

Veronika Bachanova, MD, PhD
University of Minnesota

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Disclosures

• No conflicts of interest to disclose

Lymphomas

• Name for group of cancers that arise when lymphocytes (cell that provide immune defense) become malignant
• Can present anywhere normal lymphocytes are found
• Presents with accumulation of malignant lymphocytes to form tumors in body, most commonly in lymphatic system (network of lymph nodes and channels that filter blood)
• 5th most common cancer in males and females

How common is lymphoma?

www.exponent.com/cancer_epidemiology

5,500
3,500
4,000
4,500
5,000

Indications for hematopoietic stem cell transplant in North America 2008 CIBMTR data

- Involvement of lymph-node (lymph-adenopathy)
- single lymph node region
- two or more lymph node regions
- Extra lymphatic (extranodal) site
- spleen
- bona marrow (peripheral blood)
- other – bone, GI tract, liver, lung, pleura, skin, kidney, any organ

Lymphoma – clinical presentation
Examples of clinical presentation of lymphoma

Normal lymph nodes and regions.

Making a diagnosis
- Tissue (most common lymph node) makes the diagnosis
- Bone marrow aspiration and core biopsy
  - Morphology
  - Flow-cytometry (Immunophenotyping)
  - Cytogenetics +/- FISH
  - Molecular testing
- Imaging

Lymphoma – diagnostic work-up

Morphology
- Flow cytometry
- Cytogenetics and FISH
- Molecular testing
- Type of lymphoma
Mantle Cell Lymphoma

Immunophenotyping (flow)
- Cell surface molecules (CD20, CD5, CD23 etc) can be detected by this method
- Stream of cells can be tagged with antibodies/fluorescent dye and passed through a laser beam
- Important to assess the differentiation stage of malignant lymphoma cell
- May have prognostic value (CLL/SLL)
- Presence of small amount of lymphoma in marrow on flow – unclear significance

Cytogenetics – conventional (karyotype)

Cytogenetics (FISH)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Chromosomal Translocation</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCL</td>
<td>t(11:14)</td>
<td>IGH/bcl1 (cyclin D)</td>
</tr>
<tr>
<td>FL</td>
<td>t(14:18)</td>
<td>IGH/bcl2</td>
</tr>
<tr>
<td>Burkitt</td>
<td>t(8:14)</td>
<td>MYC/IGH</td>
</tr>
<tr>
<td>T-cell NHL</td>
<td>t(2:5)</td>
<td>ALK/NPM</td>
</tr>
</tbody>
</table>

Molecular testing in lymphoma
- Not commonly used
- B-cell and T-cell heavy immunoglobulin gene rearrangement (ASO PCR) - the most common
- Not critical in evaluation of response
- "Molecular testing" in BMBx reports or Initial BMT evaluation physician note
Initial disease assessment

• History: esp B symptoms
• Good exam with Lymph node measurements
• Karnofsky performance status
• CT Scan Neck/C/A/Pelvis – Lymph Node, spleen with exact measurements
• PET scan
• Marrow Biopsy
• LDH
• CBC, LFTs, creatinin
• Sometimes EGD, ENT examination, MRI (for example CNS)

Staging: PET/CT scan

- 18fluorodeoxy-glucose (FDG) a radio-isotope is injected iv and avidly taken up by lymphoma
- More sensitive than CT scan
- Different types of lymphoma have varying PET avidity (DLBCL, mantle cell, HL, FL are PET avid) others may be PET not-avid
- Not all PET-positive lesions automatically mean they are involved by lymphoma

Staging at Time of Diagnosis

Staging defines how widespread the disease is and the locations of the disease in the body.

A: absence of B symptoms
B: fever, night sweats, weight loss

Lymphoma histology: 2 main subtypes HL and NHL

Pathology of Hodgkin lymphoma

Reed Sternberg cells:
- large, bi- or multi-nucleated, abundant cytoplasm, two or more nuclei.
- Surrounded by an inflammatory response.
Reed-Sternberg cell

Classification of HL
World Health Organization (WHO)

- Nodular lymphocyte predominant
- Classical HL
  - Nodular sclerosis
  - Mixed cellularity
  - Lymphocyte-rich
  - Lymphocyte depleted

Classifications:
- Nodular Sclerosis
- Mixed cellularity

How does HL differ from NHL?

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>HL</th>
<th>NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age</td>
<td>40s (bimodal)</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Cases / yr</td>
<td>8,000</td>
<td>60,000</td>
</tr>
<tr>
<td>Common sites</td>
<td>Neck, mediastinum</td>
<td>Various</td>
</tr>
<tr>
<td>S/Sx</td>
<td>Usually mild</td>
<td>Often severe</td>
</tr>
<tr>
<td>5 yr Survival</td>
<td>80+%</td>
<td>Varies</td>
</tr>
</tbody>
</table>

Therapy of HL

- Highly curable with chemotherapy and XRT (over 80%)
- Therapy determined principally by stage
  - Localized disease: 2-4 cycles of chemotherapy or XRT
  - Widespread disease treated with 6-8 cycles systemic chemotherapy
- Patients who do not respond completely with initial therapy or respond and then relapse need a transplant
  - Auto HCT is standard
  - Patients who relapse after an auto HCT, or have very aggressive disease requiring multiple therapies to achieve a remission may be considered for allo HCT

1st line regimen for HL: ABVD x 4-8 cycles
- Adriamycin
- Bleomycin
- Vinblastine
- Dacarbazine
  - Day 14 and day 28

Treatment of relapsed HL

- 2nd line and “salvage” chemotherapy
- Administered until response is achieved (2 or more cycles)
- Goal to induce remission and prepare for transplant
- MOPP (nitrogen mustard, Oncovir, Prednisone, Procarbazine)
- ICE (Ifosfamide, Carboplatin, Etoposide)
- DHAP (Dexamethasone, High dose Cytarabine, Cisplatin)
- Doxil, Gemcitabine, Vinorelbine
- ESHAP

Treatment of Hodgkin lymphoma

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- DHAP (Dexamethasone, High dose Cytarabine, Cisplatin)
- Doxil, Gemcitabine, Vinorelbine
- ESHAP
Lymphoma Response Criteria

- Revised "Chesson criteria" – 2007
- **Complete remission**
  - 1) no signs or symptoms of disease;
  - 2) **PET negative** in a PET-avid lymphoma
    or **CT negative** in Non PET –avid lymphoma
  - 3) Normal bone marrow by morphology and
    immunohistochemistry
- **Complete remission unconfirmed (CRu)** – if abnormalities persist on CT

Lymphoma response criteria

- **Partial remission**
  - 1) > 50% decrease in tumor size, but PET+ at prior PA sites
  - 2) > 50% decrease in tumor size, but CT+ and PET- if PET negative prior to treatment.
  - 3) Bone marrow is irrelevant if positive pre-treatment.
- **Stable disease is neither PR nor progressive disease**

Hodgkin Lymphoma

- Improved PFS after auto HCT in relapsed HL
- Relapse remains most common cause of treatment failure

Lymphoma histology – Non-Hodgkin lymphoma

Response to therapy

Complete remission in patients with PET-avid Non-Hodgkin lymphoma

PET response

CT response – tumor measurements

Lymphoma response criteria

- **Progressive/ relapsed disease** requires > 50% increase in disease or new lesions that are PET+ if PET-avid lymphoma.
- PET does not replace a biopsy before initiating new therapy!
**WHO Classification of NHL (2008)**

- DLCL 31%
- MALT 5%
- Peripheral T-cell 6%
- Small lymphocytic 6%
- Mantle cell 6%
- Other 12%
- Lymphoblastic 2%
- Burkitt-like 2%
- Mediastinal B-cell 2%
- Lymphoplasmacytic 1%
- Anaplastic T-cell 2%
- Burkitt <1%

**Lymphoma histology – Non-Hodgkin lymphoma**

<table>
<thead>
<tr>
<th>Category</th>
<th>Survival</th>
<th>Cure</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolent NHL</td>
<td>Slow</td>
<td>Years</td>
<td>Generally not curable</td>
</tr>
<tr>
<td>Intermediate NHL</td>
<td>Rapid clinical course</td>
<td>Months</td>
<td>Curable in over 50%</td>
</tr>
<tr>
<td>Aggressive NHL</td>
<td>Very aggressive</td>
<td>Weeks</td>
<td>Curable in some</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>All types</td>
<td>Variable – months to years</td>
<td>Highly curable with chemotx</td>
</tr>
</tbody>
</table>

**REAL/WHO Classifications for B-Cell Neoplasms**

<table>
<thead>
<tr>
<th>Indolent (Low Risk)</th>
<th>Aggressive (Intermediate Risk)</th>
<th>Very Aggressive (High Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
<td>Follicular lymphoma, grade III (IWF:D)</td>
<td>Burkitt's lymphoma</td>
</tr>
<tr>
<td>Splenic marginal zone lymphoma</td>
<td>PLL</td>
<td></td>
</tr>
<tr>
<td>Marginal zone B-cell lymphoma</td>
<td>Mantle cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Extramedullary</td>
<td>DLBCL</td>
<td>Primary effusion lymphoma</td>
</tr>
<tr>
<td>Nodal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytoma lymphoma, grades I-II (IWF:B-C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLL/BLL* (IWF:A)</td>
<td></td>
<td></td>
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<tr>
<td>Hairy cell leukemia</td>
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<td></td>
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</tbody>
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**AutoHCT for Lymphoma and CLL in the US CIBMTR 2002 - 2007**

Total Autologous HCT: 14,368

**AlloHCT for Lymphoma and CLL in the US CIBMTR 2002 - 2007**

Total Allogeneic HCT: 3,887

[www.cibmtr.org](http://www.cibmtr.org)


Diffuse large B cell lymphoma

- Rare
- Very distinct presentation
- Rapidly fatal
- Over 90%

Overview of DLBCL

- Patients typically present with a rapidly enlarging mass
  - ~1/3 present with B symptoms
  - ~1/3 present with stage IV disease
  - More than 2/3 have any extranodal site
  - ~1/3 have >1 extranodal site
  - ~1/6 present with bone marrow involvement
- DLBCL is rapidly progressive if not treated
  - It follows a rapid clinical course
  - 75%-80% of patients respond well to treatment

International Prognostic Index (IPI) for Aggressive NHL

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Low</th>
<th>Low-intermediate</th>
<th>High-intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≤60 vs &gt;60 years)</td>
<td>0-1</td>
<td>2-3</td>
<td>3-5</td>
<td>4-5</td>
</tr>
<tr>
<td>Performance status (0 or 1 vs ≥2)</td>
<td>0-2</td>
<td>3</td>
<td>4-5</td>
<td>6-8</td>
</tr>
<tr>
<td>LDH (≤ normal vs &gt; normal)</td>
<td>0-2</td>
<td>3</td>
<td>4-5</td>
<td>6-8</td>
</tr>
<tr>
<td>Extraneous sites (≤1 vs &gt;1)</td>
<td>0-2</td>
<td>3</td>
<td>4-5</td>
<td>6-8</td>
</tr>
<tr>
<td>Stage (I or II vs III or IV)</td>
<td>0-2</td>
<td>3</td>
<td>4-5</td>
<td>6-8</td>
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Age-adjusted criteria (patients ≤60 years)

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<td>Performance status (0 or 1 vs ≥2)</td>
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Diffuse Large B-Cell Lymphoma

- 30-70% patients are cured with chemotherapy +/- adjunctive radiation for “bulky disease”
  - 1st line therapy: R-CHOP x 6-8 cycles q 21 days (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, Rituximab)
- Relapsed lymphoma – 2nd line therapy
  - Numerous programs: R-ICE, R-DHAP, R-HyperCVAD, ESHAP
- Second remission is typically followed by autologous transplant
- Allogeneic transplant is used less common
  - relapse after autologous HCT or contraindications to autologous HCT

Immunotherapies – target surface antigens

- CD20
- CD52

Radioimmunotherapy in the Treatment of NHL

- Ibritumomab (Zevalin)
- Tositumomab (Bexxar)

- Chelator
- Radionuclide
**Autologous HCT for NHL**

Outcomes of 109 patients with relapsed, chemotherapy sensitive NHL receiving either conventional treatment (DHAP x4 ± IFRT) or autologous BMT with BEAC ± IFRT.

Philip, NEJM 1995; 333: 1540

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**Probability of survival after autologous transplant for diffuse large B-cell lymphoma, by disease status, 2000-2008**

Chemosensitive (N=6,203)

Chemoresistant (N=447)

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**Probability of survival after HLA-matched sibling donor allogeneic transplant for diffuse large B-cell lymphoma, by disease status and conditioning regimen, 1998-2008**

Chemoresistant, myeloablative (N=43)

Chemosensitive, myeloablative (N=122)

Chemosensitive, reduced-intensity conditioning (N=42)

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**Diffuse large B cell lymphoma**

- Rare
- Distinct presentation
- Rapidly fatal

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**16. Intravascular large B cell lymphoma**

- Intravascular "plugs" composed of large atypical CD20 B cells with aberrant expression of CD5
- Rare lymphoma, always extranodal, remarkable sparing of lymph nodes and bone marrow
- Challenging to diagnose
- Skin, CNS, no tumors formed

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**17. Primary mediastinal diffuse large B cell lymphoma**

At diagnosis

After Chemoth

Primary mediastinal DLBCL. 36 yo female, before and after R-CHOP. At diagnosis can see the mass penetrating through the anterior chest wall and bilateral (R>L) pleural effusion. Achieved CR with R-CHOP, went on to receive auto PBSC and consolidative XRT.
18. DLBCL - primary effusion type

- Distinct category due to atypical presentation, phenotype
- Is rare and rapidly fatal
- Presents with malignant peritoneal, pericardial or pleural effusions in absence of identifiable tumor mass or nodal involvement

Malignant effusion
Malignant large cells
Herpes virus 8 and EBV often +


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Follicular Non-Hodgkin lymphoma

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Follicular Lymphoma Histology

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of centroblasts (large cells) increase with grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criteria for grading*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1: 0-5 centroblasts/hpf, centrocytes predominate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2: 6-15 centroblasts/hpf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3: &gt;15 centroblasts/hpf</td>
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Therapy of Indolent NHL

- Don’t treat unless forced to
  - Low blood counts, B-symptoms, large masses
- As little therapy as possible
  - Monoclonal antibody therapy
    (Rituximab – anti CD20, radioimmunotherapies)
  - Chemotherapy (single agent or combinations) often achieve durable remissions
- Survival often measured in years to decades

Outcomes of Indolent NHL

- Incurable with chemo/immunotherapy
- Patients may respond to several therapies over time
- Length of first remission may give additional clue to patient’s future course

Survival After Auto HCT for Follicular Lymphoma 2000–2006

Chemosensitive (N=1,605)

Probability of Survival %

P = .0002.
Probability of survival after HLA-matched sibling donor allogeneic transplant for follicular lymphoma, by disease status and conditioning regimen, 1998-2008

- Chemosensitive, reduced-intensity conditioning (N=388)
- Chemoresistant, reduced-intensity conditioning (N=64)
- Chemosensitive, myeloablative (N=351)
- Chemoresistant, myeloablative (N=85)

Probability of survival %

Response to Pre HSCT Therapy!!

- Start and Stop Date
- Response date
- Relapse?

Pre-transplant disease assessment

- PET-avid lymphoma
- no PET-avid lymphoma

Measurements from CT scan prior to HCT

Pre-HCT remission state assessment

- Pre-transplant disease status - Terms
- Where is disease at?
  - PIF – never had a CR
  - CR (Cru) – can be 1, 2, 3+
  - REL – can be 1, 2, 3+</p>

- Pre-HCT remission state - How did it respond?
  - Sensitive
  - Resistant
  - Untreated/Unknown

- CR (Cru) – has to be sensitive!
- PIF – can be sens, res, unt/unk
- REL – can be sens/res/unt/unk

Pre HSCT disease status - Terms

- PIF Sens → a PR to initial treatment then Tx = PR
- Relt Sens → CR, Relapse then PR to chemo pre transplant

Rarely used – only 2 tests:
- T and B cell heavy chain re-arrangement
Concept of histologic transformation

Small lymphocytic lymphoma/chronic lymphocytic leukemia

- Most common leukemia
- B-cell accumulation in bone marrow and lymph nodes
- Chronic indolent disease, survival is many years
- Treatment is required only if symptoms occur
- Major complication is transformation into aggressive lymphoma (3-15%)

Richter’s transformation

- Aggressive Lymphoma (usually NHL) which arise from indolent NHL or CLL
- Present with rapidly growing mass and frequently B symptoms
- Require tissue diagnosis for confirmation (use this for date of transformation)

FISH (Fluorescent in situ hybridization) profiling in CLL

- Chromosomal abnormalities in CLL are common and have prognostic significance

Cytogenetics and FISH in CLL

Cytogenetics is Important!

Where do I look for these?

Addendum to marrow reports
Peripheral Blood FISH
Karyotype
Initial Consult note at Transplant Center
Thank you