Lymphoma Disease Management

Overview and Principles of Therapy

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Lymphoma Overview and Principles of Therapy

• Non-Hodgkin’s Lymphoma
  – Epidemiology
  – Classification/Staging
  – Indolent Lymphoma
  – Aggressive Lymphoma
• Hodgkin’s Disease – Not Today
• New Approaches to Therapy – Not Today

What is Lymphoma?

• Non-Hodgkin’s Lymphoma
  – Typically presents with a clonal expansion of lymphocytes in lymph nodes
  – Different lymphomas arise from B, T, and NK cells
  – 85% of all lymphomas in the US are derived from B cells
  – Estimated 55,000 new cases
  – Indolent lymphomas account for approximately 40% of new diagnoses
  – Aggressive lymphomas account for 60% of presentations
• Hodgkin’s Disease
  – Lymph nodes are involved with the characteristic Reed-Sternberg cells
  – Evidence suggest origin from a post germinal center B cell
  – Estimated 7,500 new cases
  – Peak of incidence in the 3rd and 4th decades of life
  – Vast majority of patients can be cured with current therapy

The Ontogeny of Lymphoid Neoplasms’ is Complex and Heterogeneous

REAL Classification of NHL Subtypes
Most Lymphomas Are Relatively Rare

WHO/REAL Classification of Lymphoma
Characteristics of the 13 Most Common Entities

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Frequency (%)</th>
<th>Immunophenotype</th>
<th>Molecular Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FL</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCL</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLL/CLL</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALT</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinal LCL</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALCL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LL (T/B)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkitt-like</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MZL (Nodal)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLL, PL</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, 16%</td>
<td></td>
<td></td>
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</tbody>
</table>

Categorizing the non-Hodgkin's Lymphomas

**Aggressive Lymphoma**
- Diffuse large B-cell NHL
- Peripheral T-cell NHL
- Burkitts lymphoma
- Lymphoblastic lymphoma
- Mantle cell lymphoma
- Approach with Curative Intent
- PBSCT Can Salvage Relapse
- Fatal if not Cured

**Indolent Lymphoma**
- Chronic lymphocytic leukemia (CLL)
- Small lymphocytic lymphoma (SLL)
- Follicular lymphoma
- Marginal Zone lymphoma
- Nodal
- Extranodal (MALTS)
- Primary splenic
- Typically Incurable
- Possible Cure for Stage 1A Disease (RT or Chemo-RT)
- Chronic Disease Manageable
- Monoclonal antibodies changing natural history

Clinical Prognostic Factors Tell Only Part of the Story

International Prognostic Index (IPI)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Age &gt;60 years</th>
<th>PS ≥ 2</th>
<th>LDH &gt; Normal</th>
<th>Extranodal sites ≥ 2</th>
<th>Stage III-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Low/Intermediate</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>High/Intermediate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

5-year DFS (%) 5-year OS (%)

- Low: 70, 73
- Low/Intermediate: 50, 51
- High/Intermediate: 40, 43
- High: 40, 26

Prognostic Subgroups in *de novo* DLBCL Based on Ontogeny

DNA microarray analysis can be used to predict survival after chemotherapy.

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- New Approaches to Therapy

International Prognostic Index Predicts Overall Survival – What is Biological Basis?


U.S. Cancer Mortality, All Ages
Non-Hodgkin’s Lymphoma: SEER Incidence by Age
1973-1975 vs 1993-1995; All Races, Male

Age at Diagnosis (years)

Rate per 100,000

140
120
100
80
60
40
20
0

1973-1975
1993-1995

0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
>85

WORLD HEALTH ORGANIZATION (WHO) T-CELL LYMPHOMA CLASSIFICATION
A Whole Different Lecture

Precursor T/NK Neoplasms
- Precursor T lymphoblastic leukemia/lymphoma
- Blastic NK lymphoma

Peripheral T/NK Neoplasms
- Predominantly leukemic/disseminated
  - T-cell prolymphocytic leukemia
  - T-cell large granular lymphocytic
  - NK/T-cell leukemia/lymphoma
  - Adult T-cell leukemia/lymphoma
- Predominantly nodal
  - Angioimmunoblastic T-cell lymphoma
  - Anaplastic large T- and NK-cell lymphoma
- (Unspecified)

Predominantly Extrahodinal
- Mycosis Fungoides (CTCL)
- Sezary syndrome
- Primary cutaneous CD30+ disorders
- Anaplastic large cell lymphoma
- Lymphomatoid papulosus
- Subcutaneous panniculitis T-cell
- NK/T-cell lymphoma
- Enteropathy-type intestinal lymphoma
- Hepatosplenic T-cell lymphoma
- Extrahodinal peripheral T/NK-cell lymphoma
- (Unspecified)

Age Distribution of Malignant Lymphoma
All Histologic Diagnoses

Data from the Royal Marsden Hospital 1962-1972.

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Clinical Staging of Lymphoma
Modified Ann Arbor Staging

- Clinical Stages
  - I: Single lymph node group
  - II: Multiple lymph node groups on one side of the diaphragm
  - III: Lymph nodes on both sides of the diaphragm
  - IV: Extra-nodal disease
- Modifiers
  - B: Fevers, night sweats, weight loss
  - A: Absence of B symptoms
  - X: Mass > 10 cm or 1/3 thoracic diameter
  - E: Extra-nodal extension of disease

B Cell Development

Clinical Staging of Lymphoma
Modified Ann Arbor Staging
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Follicular Lymphoma

H&E

CD10

CD3

CD 10+, CD 19+, CD 20+, CD 22+, LCA+, κ/λ clonal excess

CD 3 -, CD 5 -, CD 15 -, CD 30 -

CLINICAL MANAGEMENT OF FOLLICULAR LYMPHOMA
In Patients With An Indication for Therapy

Indolent NHL In Need of Treatment

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Biological</th>
<th>Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylator Rx</td>
<td>Specific</td>
<td>Autologous</td>
</tr>
<tr>
<td>COP/CHOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorambucil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purine Analog Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludarabine</td>
<td></td>
<td>Autologous</td>
</tr>
<tr>
<td>Flu / CyFlu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigational</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FL: Reproducibility of Grading
Berard Criteria

Grade 1
Small Cleaved

Grade 2
Mixed

Grade 3
Large Cell

Large Cells
Per High Power Field
<5
5-15
>15

Expert Concordance
72%
61%
60%

Indolent B-Cell Lymphoma
Survival by Era

1987-1996 (N=688)
1976-1987 (N=513)
1960-1976 (N=195)

- Molecular
  - t(14;18) translocation
  - BCL2 is overexpressed
  - BCL2 is anti-apoptotic
- Clinical
  - Equal number of men and women
  - Uncommon in Blacks and Asians
  - Transformation is common
  - Spontaneous regress occurs in ~30% of cases
- Pathology
  - subtypes: Grades 1, 2, 3

Courtesy of Sandra J. Horning, MD.
**Follicular Lymphoma**

**Histological Transformation (HT)**

- Actuarial risk of HT is 25% to 60% at 8 years
- HT results from genetic alteration of a single cell
  - P53 mutation (~50%), translocations of c-myc (~15%) and BCL6 (~10%)
- Prognosis following HT is generally poor

**Indolent B Cell Lymphoma**

**Clinical Management**

- **Localized**
  - Observation

- **Advanced**
  - Low Tumor Burden: Therapy
  - High Tumor Burden: Therapy

**Gastric MALT Lymphoma**

**A curable low grade lymphoma**

- Strong association with *Helicobacter pylori* infection
  - In 10%-50% of cases, treatment of the infection will result in regression of the lymphoma
  - Remissions may take up to 6 months
- Most patients who fail to respond to antibiotics can be cured with radiation therapy

**Disease-Free Survival**

- N = 48 patients
- 80% survival at 6 years

**Indolent B Cell Lymphoma: Advanced Stage**

**Principles of Therapy**

- Not curable with conventional therapy
- Presents in older patients who may have significant co-morbid conditions complicating therapeutic options
- Observation is appropriate if there are no indications for therapy
- Response duration is generally shorter with each course of therapy
- Enrollment on clinical trials is recommended if feasible
Indolent B Cell Lymphoma: Advanced Stage
Observation in Absence of an Indication for Treatment

- Both prospective randomized and retrospective studies have:
  - No survival disadvantage
  - 3 year median progression to treatment
  - Same rate of histological transformation

TARGETS ON B-CELLS

- Surface proteins can be targeted with:
  - Active immunotherapy
  - Vaccines
  - Passive immunotherapy
  - Unmodified MAbs
  - Conjugated MAbs
  - Radioimmunoconjugates
  - Drugs
  - Toxins
  - Peptides selected for binding
  - Small molecules

Indolent B Cell Lymphoma: Advanced Stage
Clinical Management

Indolent B Cell Lymphoma

- Localized
- Advanced
- Low Tumor Burden
- Advanced
- High Tumor Burden

- Involved/Extended Field Radiation
- Observation
- Therapy

Indolent B Cell Lymphoma: Advanced Stage
Clinical Management with Indication for Therapy

B-Cell Life Cycle
CD20 Tumor Specificity

B1 (CD20) Antigen

- TARGETS ON B-CELLS
- Indolent B Cell Lymphoma: Advanced Stage
- Observation in Absence of an Indication for Treatment
- Localized
- Advanced
- Low Tumor Burden
- Advanced
- High Tumor Burden
- Involved/Extended Field Radiation
- Observation
- Therapy
- B-Cell Life Cycle
- CD20 Tumor Specificity
- B1 (CD20) Antigen
**Cytotoxic Mechanisms of Monoclonal Antibodies**

- Effector cells/complement
- Apoptosis
- Radiation/radionuclide
- Toxin/drug

**Crossfire Enhances Antibody Action**

- Naked Antibody
- Radiolabeled Antibody

**RITUXIMAB CLINICAL TRIAL SUMMARY LOW GRADE LYMPHOMA**

<table>
<thead>
<tr>
<th>Trial Phase</th>
<th>Patient Population</th>
<th>Regimen</th>
<th>RR</th>
<th>RD</th>
<th>TTP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal, Phase III</td>
<td>Low grade NHL, relapsed/refractory</td>
<td>Rituximab 375 mg/m² x 4</td>
<td>48%</td>
<td>6%</td>
<td>11.2</td>
</tr>
<tr>
<td>Phase II</td>
<td>Low grade NHL, new dx or relapsed/refractory</td>
<td>Rituximab 375 mg/m² x 6, CHOP x 6</td>
<td>95%</td>
<td>55%</td>
<td>39.1+</td>
</tr>
</tbody>
</table>

- RR: Response Rate
- ORR: Overall Response Rate
- CR: Complete response
- PR: Partial Response
- RD: Response Duration
- TTP: Time to tumor progression

**Rituximab**
- Engineered derivative of IDEC-2B8
- Murine antigen binding domain
- Human κ constant region
- Human IgG1 constant region
- Induces apoptosis

**CD20 antigen**
- Hydrophobic, 35 kD phosphoprotein
- Expressed only on B lineage cells
- Important for cell cycle initiation and differentiation
- Does not shed or rapidly modulate off cell surface

**Effect of chimerism**
- $t_1/2 = 76$ h after 1st dose
- $t_1/2 = 206$ h after 4th dose
- Activates complement
- Induces antibody dependent cell-mediated cytotoxicity

**Ibritumomab tiuxetan**
- Murine IDEC-2B8 (parent of rituximab)
- MX-DTPA conjugated to antibody forming strong urea-type bond
- Stable retention of $^{90}$Y

**Yttrium-90**
- $t_1/2 = 64$ hours
- Outpatient administration
- Beta emission
- $X_{eq} = 5$ mm
**Iodine I 131 Tositumomab**  
**Mechanism Of Action**

- Iodine I 131 tositumomab  
  - murine IgG2a anti-CD20 MAb  
  - B-cell specific  
  - triggers apoptosis  
  - antibody-dependent cellular cytotoxicity  
- Iodine-131 radionuclide  
  - beta emission  
  - short pathlength "crossfire" effect (~1mm)  
  - gamma emission  
  - allows individual dosimetry  
- Iodine I 131 tositumomab  
  - targeted radiotherapy

**Indolent Lymphoma**  
**Continuing Challenges**

- Define the optimal use of antibody-based therapy  
  - First line  
  - In combination with chemotherapy  
  - Sequentially with chemotherapy  
- Refine the use of high dose therapy to provide maximal benefit  
- Develop new targeted therapy based on molecular mechanisms of lymphomagenesis

**RITUXIMAB v 90Y-2B8: RESPONSE TO THERAPY**  
**INTERIM ANALYSIS (n=90)**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Rituximab N (%)</th>
<th>Ibritumomab N (%)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>20 (43.5)</td>
<td>35 (79.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>CR</td>
<td>3 (7%)</td>
<td>9 (21)</td>
<td>0.057</td>
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<tr>
<td>PR</td>
<td>17 (37%)</td>
<td>26 (59%)</td>
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</tbody>
</table>

*Calculated from Cochran-Mantel-Haenszel test over histology type (A/Follicular/Transformed)

Witzig, et al., Blood, 94 (Supplement 1), Abstract 2805

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**Overall Survival: Large Cell Histologies**

- Anaplastic large cell lymphoma  
- Diffuse large B cell lymphoma  
- Burkitt-Like  
- Peripheral T cell lymphoma

Log rank test: p<0.001

Witzig, et al., Blood, 94 (Supplement 1), Abstract 2805
Three Generations of Chemotherapy for NHL: Apparent Improvement in Outcome

<table>
<thead>
<tr>
<th>DFS: 55-45%</th>
<th>DFS: 50-70%</th>
<th>DFS: 60-75%</th>
</tr>
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<tbody>
<tr>
<td>BACOP</td>
<td>ProMACE-MOPP</td>
<td>MACOP-B</td>
</tr>
<tr>
<td>MOPP</td>
<td>M-BACOD</td>
<td>ProMACE-CytaBOM</td>
</tr>
<tr>
<td>COPA-Bleo</td>
<td>COP-BLAM</td>
<td>ProMACE-MOPP 1/8</td>
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<tr>
<td>CAP-BOP</td>
<td></td>
<td>COP-BLAM III</td>
</tr>
<tr>
<td>COMLA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP</td>
<td></td>
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</table>

National High Priority Lymphoma Study: Time to Treatment Failure by Randomized Treatment Arm

International Prognostic Index Age-Adjusted (aIPI)

- Prognostic Indicators (PLS)
  - Performance status > 1
  - LDH > 1 x normal
  - Stage III or IV
- Risk Category Factors
  - Low
  - Low-intermediate
  - High-intermediate
  - High

International Prognostic Index

- Prognostic Indicators (APLES)
  - Age > 60 years
  - Performance status > 1
  - LDH > 1 x normal
  - Extranodal sites > 1
  - Stage III or IV
- Risk Category Factors
  - Low 0 or 1
  - Low-intermediate 2
  - High-intermediate 3
  - High 4 or 5

Diffuse Large B Cell Lymphoma
Distinct Forms Revealed by Expression Arrays

- Lymphochip expression array data segregates diffuse large B cell lymphoma into two molecular entities:
  - Germinal center phenotype
  - Activated B cell phenotype
- Molecular subtype is independent of International Prognostic Index risk group
Management of Aggressive NHL

- R-CHOP
  - 55
  - 45
- CR
- Primary Refractory
- Cure
- Relapse
- HDT/ASCT

Parma Trial: Event-free Survival

- % Event-free Survival
- Months from Inclusion

- ABMT (N = 55)
- DHAP (N = 54)

Second Line Therapy for Aggressive NHL

- Ideal second line therapy
  - Provides effective reduction in tumor size
  - Results in minimal non-hematologic toxicity
  - Effectively mobilizes stem cells into the peripheral blood

Aggressive Lymphoma

Second-line Therapy

Therapy for Aggressive NHL Summary

- R-CHOP remains the standard, albeit with suboptimal results, for refractory NHL
- Passive Immunotherapy in aggressive NHL has changed the landscape
- High dose therapy with ASCT is superior to chemotherapy for relapsed and refractory aggressive lymphoma
- A better response to second line therapy correlates with a superior outcome post ASCT
- Based on intention to treat, about 30% of patients are benefited by second-line therapy with high dose chemotherapy consolidation
Therapy for Aggressive NHL

Summary

- Patients with primary refractory disease, both induction failures and those achieving only a PR to first line therapy can benefit from ASCT
- Second-line age-adjusted international prognostic index (saalPI) predicts survival
- Not all patients with relapsed and refractory aggressive NHL are potentially curable with this approach, particularly:
  - relapsed saalPI IV
  - refractory saalPI III/IV

Second-line Therapy of NHL

Avenues for New Directions

- Improved cytoreduction (RICE)
- Improved HDT (TBI-Ifos-Etop)
  - Non-myeloablative alloBMT
- Post remission therapy
  - Cellular therapy
  - Post remission chemotherapy (after transduction of stem cells with drug resistance genes)
- Novel targeted therapy

The Future of Cancer Therapy

Targeting the Molecular Pathways