Lymphoma Disease Management

Overview and Principles of Therapy

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Herbert Irving Comprehensive Cancer Center
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Columbia University Medical Center

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
The Ontogeny of Lymphoid Neoplasm’s is Complex and Heterogeneous

V(D)J Recombination  IgV hypermutation  Ig isotype switch

Immature B-cells  Naive B-cells  Germinal Center B-cells  Memory B-cells

Bone Marrow  Ag  Mantle  Germinal Center

ALL  MCL  BL FL DLBCL  MM

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
REAL Classification of NHL Subtypes
Most Lymphomas Are Relatively Rare

![Pie chart showing the distribution of NHL subtypes. DLBCL is 31%, MCL is 6%, and other subtypes account for 16%.]

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>DLCL</td>
<td>31</td>
<td>CD20+</td>
<td>BCL2, BCL6, CMYC</td>
</tr>
<tr>
<td>FL</td>
<td>22</td>
<td>CD20+, CD10+, CD5-</td>
<td>BCL2</td>
</tr>
<tr>
<td>SLL/CLL</td>
<td>6</td>
<td>CD20 weak, CD5+, CD23+</td>
<td>+12, del(13q)</td>
</tr>
<tr>
<td>MCL</td>
<td>6</td>
<td>CD20+, CD5+, CD23-</td>
<td>CYCLIN D1</td>
</tr>
<tr>
<td>PTCL</td>
<td>6</td>
<td>CD20-, CD3+</td>
<td>Variable</td>
</tr>
<tr>
<td>MZL (MALT)</td>
<td>5</td>
<td>CD20+, CD5-, CD23-</td>
<td>BCL10, +3, +18</td>
</tr>
<tr>
<td>Mediastinal LCL</td>
<td>2</td>
<td>CD20+</td>
<td>Variable</td>
</tr>
<tr>
<td>ALCL</td>
<td>2</td>
<td>CD20-, CD3+, CD30+, CD15-, EMA+</td>
<td>ALK</td>
</tr>
<tr>
<td>LL (T/B)</td>
<td>2</td>
<td>T cell CD3+, B cell CD19+</td>
<td>Variable, TCL1-3</td>
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<tr>
<td>Burkitt-like</td>
<td>2</td>
<td>CD20+, CD10-, CD5-</td>
<td>CMYC, BCL2</td>
</tr>
<tr>
<td>MZL (Nodal)</td>
<td>1</td>
<td>CD20+, CD10-, CD23-, CD5-</td>
<td>+3, +18</td>
</tr>
<tr>
<td>SLL, PL</td>
<td>&lt;1</td>
<td>CD20+, clg+, CD5-, CD23-</td>
<td>PAX-5</td>
</tr>
<tr>
<td>BL</td>
<td>&lt;1</td>
<td>CD20+, CD10+, CD5-</td>
<td>CMYC</td>
</tr>
<tr>
<td>TOTAL</td>
<td>88</td>
<td></td>
<td></td>
</tr>
</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

**Indolent Lymphoma**
- Chronic lymphocytic leukemia (CLL)
- Small lymphocytic lymphoma (SLL)
- Follicular lymphoma
- Marginal Zone lymphoma
  - Nodal
  - Extranodal (MALTS)
  - Primary splenic

**Approach with Curative Intent**
- PBSCT Can Salvage Relapse
- 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>Adverse</th>
<th>Risk Group</th>
<th>Number of Factors Present</th>
<th>5-year DFS (%)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 years</td>
<td></td>
<td>Low</td>
<td>0-1</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>PS ≥2</td>
<td></td>
<td>Low/Intermediate</td>
<td>2</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>LDH &gt;Normal</td>
<td></td>
<td>High/Intermediate</td>
<td>3</td>
<td>49</td>
<td>43</td>
</tr>
<tr>
<td>Extranodal sites ≥2</td>
<td></td>
<td>High</td>
<td>4-5</td>
<td>40</td>
<td>26</td>
</tr>
</tbody>
</table>

**Age-Adjusted**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adverse</th>
<th>Risk Group</th>
<th>Number of Factors Present</th>
<th>5-year DFS (%)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS ≥2</td>
<td></td>
<td>Low</td>
<td>0</td>
<td>56</td>
<td>83</td>
</tr>
<tr>
<td>LDH &gt;Normal</td>
<td></td>
<td>Low/Intermediate</td>
<td>1</td>
<td>44</td>
<td>69</td>
</tr>
<tr>
<td>Stage III-IV</td>
<td></td>
<td>High/Intermediate</td>
<td>2</td>
<td>37</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>3</td>
<td>21</td>
<td>32</td>
</tr>
</tbody>
</table>

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

Prognostic Subgroups in de novo DLBCL Based on Ontogeny

DNA microarray analysis can be used to predict survival after chemotherapy

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  – Indolent Lymphoma
  – Aggressive Lymphoma

• Hodgkin’s Disease

• New Approaches to Therapy

U.S. Cancer Mortality, All Ages

All sites -2.6
Lung -1.5
Breast (women) -6.3
Prostate -6.2
Colorectal -5.4
Ovary -4.8
Cervix Uteri -9.7
Bladder -1.5
Oral -9.6
Lymphatic 3.8
Leukemias -1.9
Other -0.9

Percent change, 1991-1995
Non-Hodgkin’s Lymphoma: SEER Incidence by Age
1973-1975 vs 1993-1995; All Races, Male

Age Distribution of Malignant Lymphoma
All Histologic Diagnoses

Data from the Royal Marsden Hospital 1962-1972.
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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

<table>
<thead>
<tr>
<th>Predominantly leukemic/disseminated</th>
<th>Predominantly Extranolad</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell prolymphocytic leukemia</td>
<td>Mycosis Fungoides (CTCL)</td>
</tr>
<tr>
<td>T-cell large granular lymphocytic</td>
<td>Sezary syndrome</td>
</tr>
<tr>
<td>NK/T-cell leukemia/lymphoma</td>
<td>Primary cutaneous CD30+ disorders</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td>Anaplastic large cell lymphoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predominantly nodal</th>
<th>Subcutaneous panniculitis T-cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>NK/T-cell lymphoma-nasal</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma</td>
<td>Enteropathy-type intestinal lymphoma</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>Hepatosplenic T-cell lymphoma (γ,δ)</td>
</tr>
<tr>
<td>(Unspecified)</td>
<td>Extranolad peripheral T/NK-cell lymphoma</td>
</tr>
<tr>
<td>(Unspecified)</td>
<td>(Unspecified)</td>
</tr>
</tbody>
</table>
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
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• New Approaches to Therapy

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

Indolent NHL In Need of Treatment

**Chemotherapy**
- Alkylator Rx
  - CVP/CHOP
  - Chlorambucil

- Purine Analog Rx
  - Fludarabine
  - FND
  - Flu / CyFlu

- Investigational

**Biological**

- **Specific**
  - Antibody Rx
  - Rituximab
  - R-CHOP/R-CVP
  - R-Flu (R & all combos w / R)
  - Radioimmuno Rx
  - Vaccines

- **Non-Specific**
  - Interferon

**Transplantation**
- Autologous
- Allogeneic
Indolent B-Cell Lymphoma
Survival by Era

![Graph showing survival rates by era with data points for 1987-1996 (N=668), 1976-1987 (N=513), and 1960-1976 (N=195).]

Follicular Lymphoma

- H&E
- CD20: CD 10+, CD 19+, CD 20+, CD 22+, LCA+, κ/λ clonal excess
- CD10
- CD3: CD 3 -, CD 5 -, CD 15 -, CD 30 -

Courtesy of Sandra J. Horning, MD.
### FL: Reproducibility of Grading

**Berard Criteria**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Cleaved</td>
<td>Mixed</td>
<td>Large Cell</td>
</tr>
<tr>
<td>Large Cells Per High Power Field</td>
<td>&lt;5</td>
<td>5-15</td>
</tr>
<tr>
<td>Expert Concordance</td>
<td>72%</td>
<td>61%</td>
</tr>
</tbody>
</table>

### Follicular Lymphoma

- **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
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

Advanced
Low Tumor Burden

Advanced
High Tumor Burden

Involved/Extended
Field Radiation

Observation

Therapy
Gastric MALT Lymphoma
A *curable* low grade lymphoma

- Strong association with *Heliobacter 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**

- Proportion Surviving
- Months
- N = 48 patients
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

Indolent B Cell Lymphoma
Clinical Management

Indolent B Cell Lymphoma

- Localized
  - Involving/Extended Field Radiation
- Advanced Low Tumor Burden
- Observation
- Advanced High Tumor Burden
  - Therapy
Indolent B Cell Lymphoma: Advanced Stage
Clinical Management with Indication for Therapy

Diagnosis of Low Grade Lymphoma
Needs Treatment

Chemotherapy-based
Alkylation Based Treatment
- e.g. CVP
- Chlorambucil

Purine Analogs
- Fludarabine
- FND
- CyFlu

B Lymphocytes
- DR
- slg
- CD19
- CD20
- CD22

TARGETS ON B-CELLS

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

Specific
- Antibody-Based
- RituXimab Alone
- CHOP+RituXimab

Non-Specific
- Interferon

Autologous
- Allogeneic
  - Full or Non-myeloablative

Radio-immunotherapy
- Tositumomab
- Ibritumomab Tiuxetan

Vaccination
B-Cell Life Cycle
CD20 Tumor Specificity

Pluripotent Stem Cell → Lymphoid Stem Cell → Pre-B Cell → B Cell → Activated B Cell → Plasma Cell

CD20 Antigen Expression

CML
Precursor B-Cell Acute Leukemias
B-Cell Lymphomas, CLL
Myeloma

B1 (CD20) Antigen

Exon VI
Exon VII
Exon VIII
Exon IV
Exon V
Exon V
Exon III
Exon II
Exon I

Extracellular
Cytoplasm
COOH
NH₂
E III
E IV

B cell

CD20 antigen

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

Cytotoxic Mechanisms of Monoclonal Antibodies

- Effector cells/complement
- Apoptosis
- Radiation/radionuclide
- Toxin/drug
# RITUXIMAB CLINICAL TRIAL SUMMARY
## LOW GRADE LYMPHOMA

<table>
<thead>
<tr>
<th>Trial Phase (Author)</th>
<th>N</th>
<th>Patient Population</th>
<th>Regimen</th>
<th>RR</th>
<th>RD Months</th>
<th>TTP (median) Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal, Phase III</td>
<td>166</td>
<td>Low grade NHL, relapsed/refractory</td>
<td>Rituximab 375 mg/m² × 4</td>
<td>ORR 48%</td>
<td>11.2</td>
<td>13+</td>
</tr>
<tr>
<td>(McLaurin et al)</td>
<td></td>
<td></td>
<td>CR 6%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PR 42%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab/CHOP-Phase II</td>
<td>40</td>
<td>Low grade NHL, new dx or relapsed/refractory</td>
<td>Rituximab 375 mg/m² × 6 CHOP x 6</td>
<td>ORR 95%</td>
<td>39.1+</td>
<td>41.1</td>
</tr>
<tr>
<td>(Czuczman et al)</td>
<td></td>
<td></td>
<td>CR 55%</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PR 40%</td>
<td></td>
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</tbody>
</table>

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

---

### External Beam Irradiation

![External Beam Irradiation Diagram]

### Radioimmunotherapy

![Radioimmunotherapy Diagram]
Crossfire Enhances Antibody Action

Naked Antibody

Radiolabeled Antibody

• 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
  – $X_{90} = 5$ 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 radioisotope
  - beta emission
    - short path length "crossfire" effect (~1mm)
    - gamma emission
      - allows individual dosimetry
- Iodine I 131 tositumomab
  - targeted radiotherapy

RITUXIMAB v ^90^Y-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>95% CI</td>
<td>28.1-58.9%</td>
<td>64.2-89.7%</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>3 (7%)</td>
<td>9 (21)</td>
<td>0.057</td>
</tr>
<tr>
<td>PR</td>
<td>17 (37%)</td>
<td>26 (59%)</td>
<td></td>
</tr>
</tbody>
</table>

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

Witzig, et al., Blood, 94 (Supplement 1), Abstract 2805
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
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- Hodgkin’s Disease

- New Approaches to Therapy

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

Years: 0 1 2 3 4 5 6 7 8 9
Survival: 0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Three Generations of Chemotherapy for NHL: Apparent Improvement in Outcome

<table>
<thead>
<tr>
<th>First Generation</th>
<th>Second Generation</th>
<th>Third Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS: 35-45%</td>
<td>DFS: 50-70%</td>
<td>DFS: 60-75%</td>
</tr>
<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>
</tr>
<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>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Years after Randomization</th>
<th>CHOP</th>
<th>M-BACOD</th>
<th>P-CytaBOM</th>
<th>MACOP-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Risk</td>
<td>225</td>
<td>223</td>
<td>233</td>
<td>218</td>
</tr>
<tr>
<td>Relapses or death</td>
<td>114</td>
<td>109</td>
<td>115</td>
<td>119</td>
</tr>
<tr>
<td>3-year estimate</td>
<td>41%</td>
<td>46%</td>
<td>46%</td>
<td>41%</td>
</tr>
</tbody>
</table>

**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

References:

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### International Prognostic Index

#### Age-Adjusted (aaIPI)

### Prognostic Indicators (PLS)
- Performance status > 1
- LDH > 1 x normal
- Stage III or IV

### Risk Category Factors
- Low 0
- Low-intermediate 1
- High-intermediate 2
- High 3

References:
**International Prognostic Index**

Age-Adjusted Overall Survival

![Graph showing survival rates for different risk groups.](image)


---

**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

CR

 Cure

Relapse

HDT/ASCT

Primary Refractory

???

Aggressive Lymphoma

Second-line Therapy
Management of Aggressive NHL

R-CHOP

CR Primary Refractory

Cure

Relapse

HDT/ASCT

Parma Trial: Event-free Survival

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

Therapy for Aggressive NHL

Summary

• R-CHOP remains the standard, albeit with suboptimal results, for refractory
• 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

TARGETING BCL-6 IN LYMPHOMA

- **BCL6**
  - HDAC
  - Ac

- **BCL6**
  - Ac
  - Ac

No Transcription

HDAC Inhibitor

Transcription (ex: p21WAF1)

Growth Inhibition, Apoptosis, Differentiation

Anti-tumor activity
The BCL6:p53 Network: A Rational Target

SAHA
HDAC inhibitor

Acetylation

Sir2 inhibitor
NIACINAMIDE

BCL6

Co-repressor complex

Small molecules

DNA damage

p53

DEATH

ETOPOSIDE

Thank You