Lymphoma Disease Management

Overview and Principles of Therapy

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What is Lymphoma?

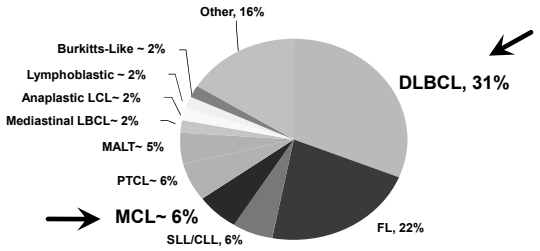
- **Non-Hodgkin's Lymphoma**
  - Typically presents with a clonal expansion of lymphocytes in lymph nodes
  - Different lymphomas arise from B, T, and NK cells
  - 85% of all lymphomas in the US are derived from B cells
  - Estimated 55,000 new cases
  - Indolent lymphomas account for approximately 40% 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

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

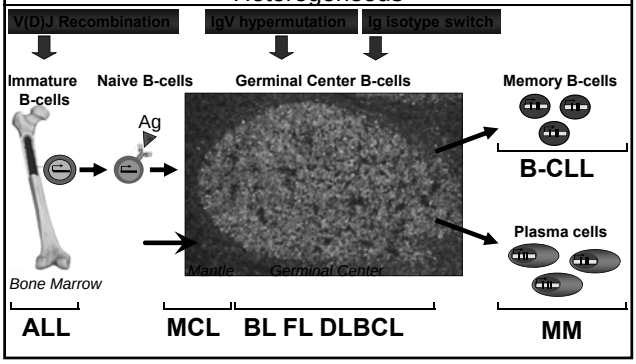
REAL Classification of NHL Subtypes

Most Lymphomas Are Relatively Rare



Armitage JO, Weisenburger DD. *J Clin Oncol*. 1998;16:2780-2795.

The Ontogeny of Lymphoid Neoplasm's is Complex and Heterogeneous



WHO/REAL Classification of Lymphoma

Characteristics of the 13 Most Common Entities

Subtype	Frequency (%)	Immunophenotype	Molecular Lesions
	31		
	22		
	6		
	6		
	6		
	5		
	2		
	2		
	2		
	2		
	1		
	1		
	<1		
	88		

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

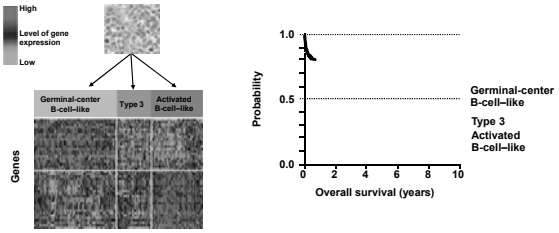
- Chronic lymphocytic leukemia (CLL)
- Small lymphocytic lymphoma (SLL)
- Follicular lymphoma
- Marginal Zone lymphoma
  - Nodal
  - Extranodal (MALTS)
  - Primary splenic

⇩

- Typically Incurable
- Possible Cure for Stage 1A Disease (RT or Chemo-RT)
- Chronic Disease Manageable
- Monoclonal antibodies changing natural history

Prognostic Subgroups in *de novo* DLBCL Based on Ontogeny

DNA microarray analysis can be used to predict survival after chemotherapy



Rosenwald A et al. *N Engl J Med.* 2002;346:1937-1947.

Clinical Prognostic Factors Tell Only Part of the Story

International Prognostic Index (IPI)

Factor	Adverse
Age	>60 years
PS	≥2
LDH	>Normal
Extranodal sites	≥2
Stage	III-IV

Risk Group	Number of Factors Present	5-year DFS (%)	5-year OS (%)
Low	0-1	70	73
Low/Intermediate	2	50	51
High/Intermediate	3	49	43
High	4-5	40	26

Age-Adjusted

Factor	Adverse
PS	≥2
LDH	>Normal
Stage	III-IV

Age-Adjusted

Risk Group	Number of Factors Present	5-year OS Age>60 (%)	5-year OS Age≤60 (%)
Low	0	56	83
Low/Intermediate	1	44	69
High/Intermediate	2	37	46
High	3	21	32

The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med.* 1993;329:987-994.

Lymphoma Overview and Principles of Therapy

- Non-Hodgkin's Lymphoma
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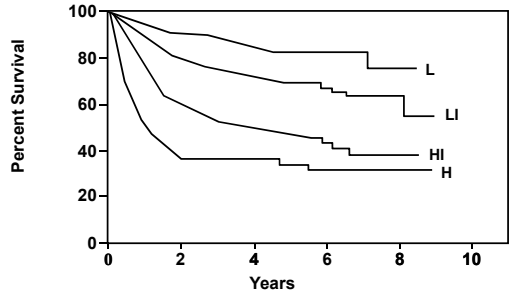
- Hodgkin's Disease
- New Approaches to Therapy

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

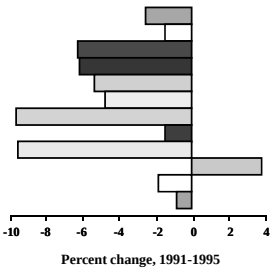


N Engl J Med.1993;329:987.

Trends in Cancer Mortality, 1991-1995

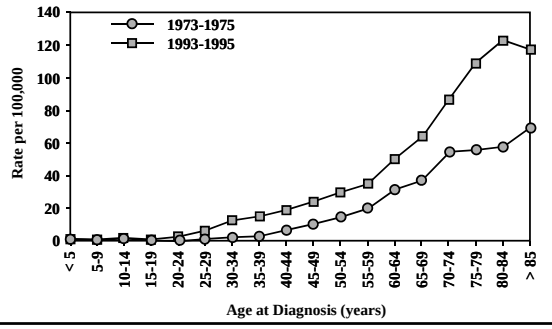
U.S. Cancer Mortality, All Ages

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



Non-Hodgkin's Lymphoma: SEER Incidence by Age

1973-1975 vs 1993-1995; All Races, Male



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 cell lymphoma
- Peripheral T-cell lymphoma (Unspecified)

Predominantly Extranodal

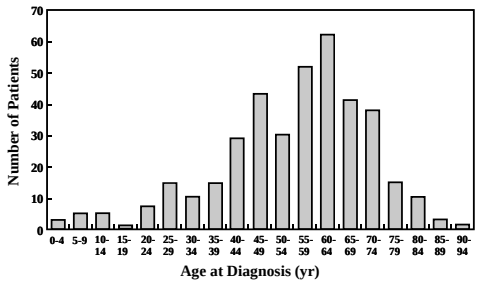
- Mycosis Fungoides (CTCL)
- Sezary syndrome
- Primary cutaneous CD30+ disorders
- Anaplastic large cell lymphoma
- Lymphomatoid papulosis

Subcutaneous panniculitis T-cell

- NK/T-cell lymphoma-nasal
- Enteropathy-type intestinal lymphoma
- Hepatosplenic T-cell lymphoma (γ,δ)
- Extranodal peripheral T/NK-cell lymphoma (Unspecified)

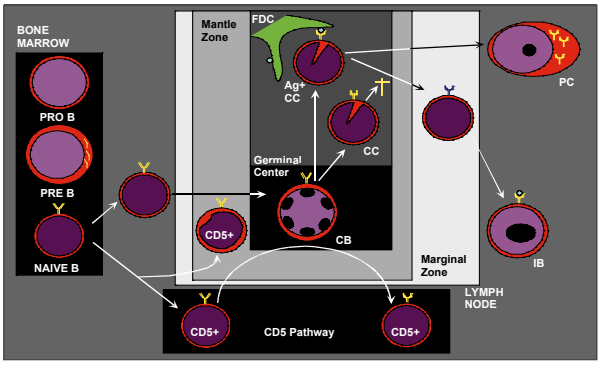
Age Distribution of Malignant Lymphoma

All Histologic Diagnoses



Data from the Royal Marsden Hospital 1962-1972.

B Cell Development



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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

Lymphoma Overview and Principles of Therapy

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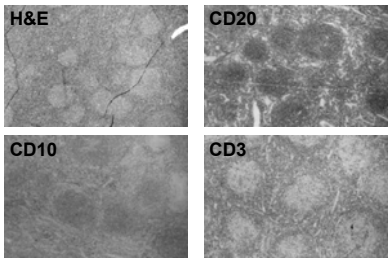
Follicular Lymphoma



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

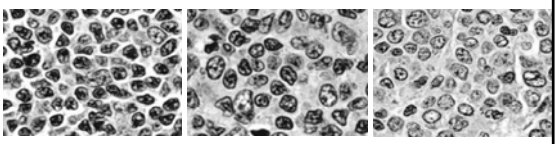
CD 3 -, CD 5 -, CD 15 -, CD 30 -

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

Indolent NHL In Need of Treatment

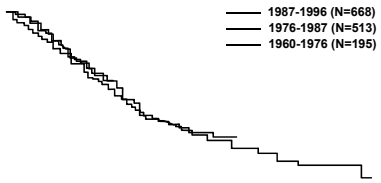
- **Chemotherapy**
  - Alkylator Rx: CVP/CHOP, Chlorambucil
  - Purine Analog Rx: Fludarabine, FND, Flu / CyFlu
  - Investigational
- **Biological**
  - Specific
    - Antibody Rx: Rituximab, R-CHOP/R-CVP, R-Flu (R & all combos w / R), Radioimmuno Rx, Vaccines
  - Non-Specific
    - Interferon
- **Transplantation**
  - Autologous
  - Allogeneic

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%

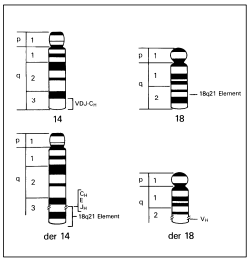
Indolent B-Cell Lymphoma
Survival by Era



Courtesy of Sandra J. Horning, MD.

Follicular Lymphoma

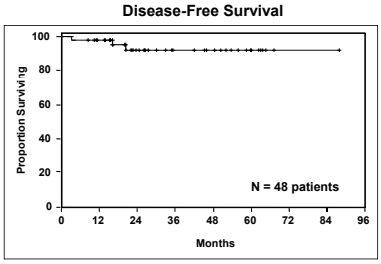
- **Molecular**
  - **t(14;18) translocation**
  - **BCL2 is overexpressed**
  - **BCL2 is anti-apoptotic**
- **Clinical**
  - **Equal number of men and women**
  - **Uncommon in Blacks and Asians**
  - **Transformation is common**
  - **Spontaneous regress occurs in ~30% of cases**
- **Pathology**
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



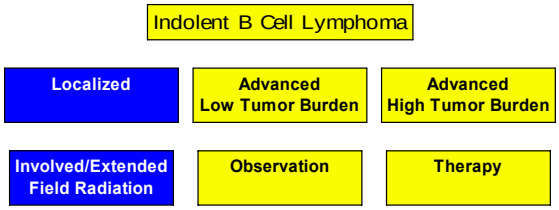
Follicular Lymphoma
Histological Transformation (HT)

- 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

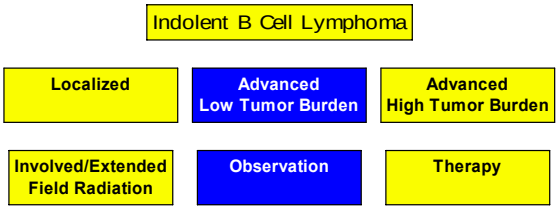
Gastric MALT Lymphoma
A *curable* low grade lymphoma



Indolent B Cell Lymphoma
Clinical Management



Indolent B Cell Lymphoma
Clinical Management



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

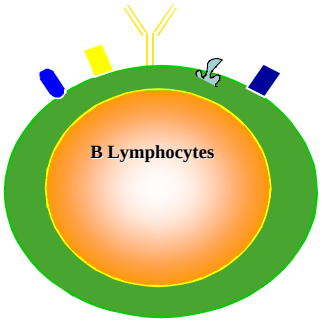
Indolent B Cell Lymphoma: Advanced Stage
Principles of Therapy

- 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

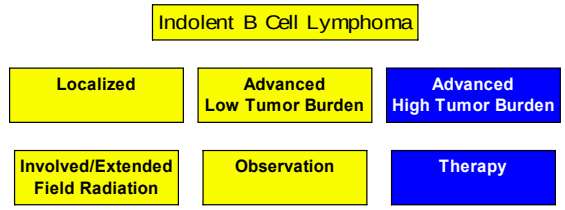
- Both prospective randomized and retrospective studies have:
  - No survival disadvantage
  - 3 year median progression to treatment
  - Same rate of histological transformation

TARGETS ON B-CELLS

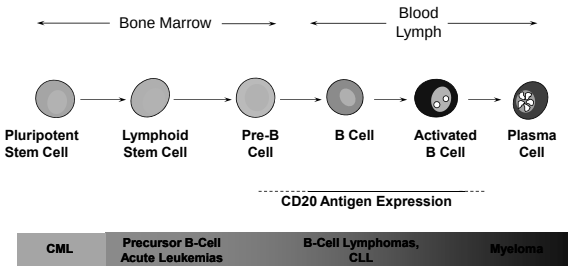


- **Surface proteins can be targeted with:**
  - **Active immunotherapy**
    - **Vaccines**
  - **Passive immunotherapy**
    - **Unmodified MAbs**
    - **Conjugated MAbs**
      - **Radioisotopes**
      - **Drugs**
      - **Toxins**
  - **Peptides selected for binding**
  - **Small molecules**

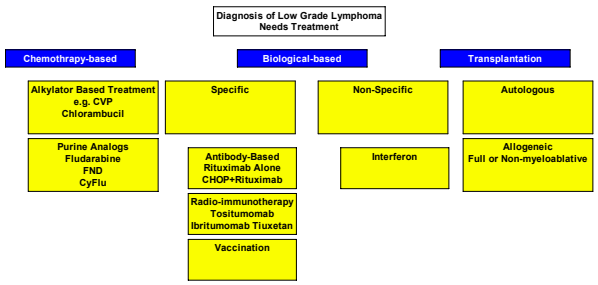
Indolent B Cell Lymphoma
Clinical Management



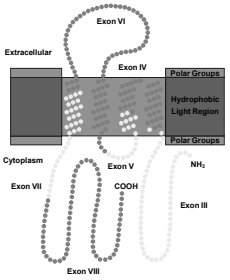
B-Cell Life Cycle
CD20 Tumor Specificity



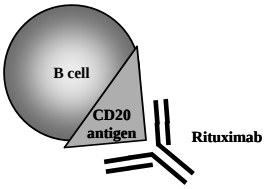
Indolent B Cell Lymphoma: Advanced Stage
Clinical Management with Indication for Therapy



B1 (CD20) Antigen



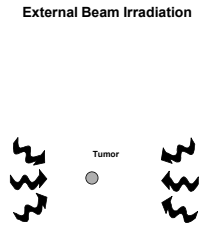
Mason et al. *Am J Pathol.* 1990;136:1215.

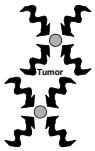


- Rituximab
  - Engineered derivative of IDEC-2B8
  - Murine antigen binding domain
  - Human κ constant region
  - Human Igγ1 constant region
  - Induces apoptosis

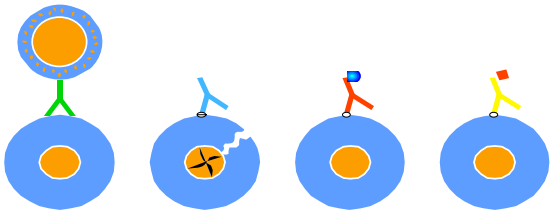
- CD20 antigen
  - Hydrophobic, 35 kD phosphoprotein
  - Expressed only on B lineage cells
  - Important for cell cycle initiation and differentiation
  - Does not shed or rapidly modulate off cell surface

- 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



Crossfire Enhances Antibody Action

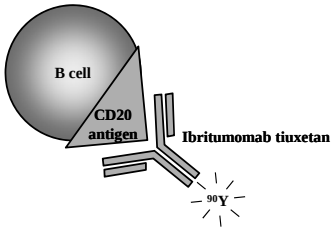
Naked Antibody

Radiolabeled Antibody

RITUXIMAB CLINICAL TRIAL SUMMARY
LOW GRADE LYMPHOMA

Trial Phase (Author)	N	Patient Population	Regimen	RR	RD Months	TTP (median) Months

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

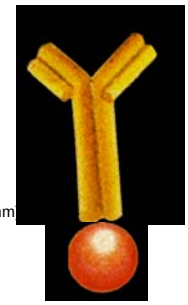


- Ibritumomab tiuxetan
  - Murine IDEC-2B8 (parent of rituximab)
  - MX-DTPA conjugated to antibody forming strong urea-type bond
  - Stable retention of ^{90}Y

- 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 $IgG2_a$ anti-CD20 MAb
  - B-cell specific
  - triggers apoptosis
  - antibody-dependent cellular cytotoxicity
- Iodine-131 radioisotope
  - 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 ^{90}Y-2B8: RESPONSE TO THERAPY
INTERIM ANALYSIS (n=90)

Histology	Rituximab N (%)	Ibritumomab N (%)	p-value*

***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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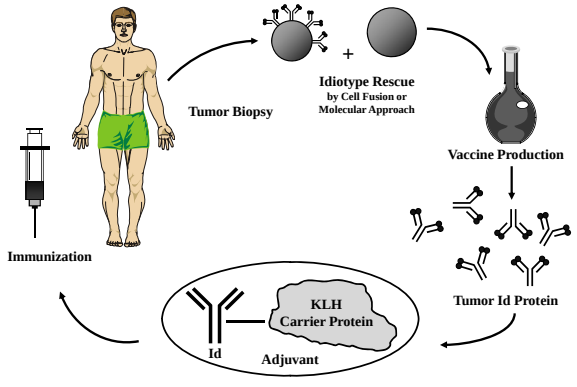
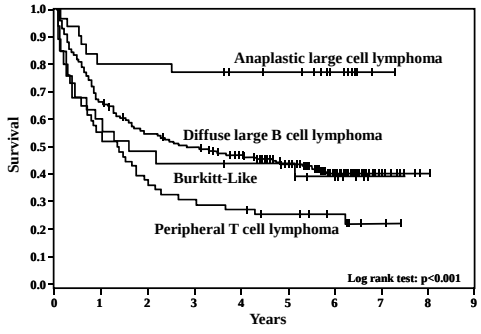


Overall Survival: Large Cell Histologies



Three Generations of Chemotherapy for NHL: Apparent Improvement in Outcome

DFS: 35-45%	DFS: 50-70%	DFS: 60-75%
BACOP	ProMACE-MOPP	MACOP-B
MOPP	M-BACOD	ProMACE-CytaBOM
COPA-Bleo	COP-BLAM	ProMACE-MOPP 1/8
CAP-BOP		COP-BLAM III
COMLA		
COPA		
CHOP		

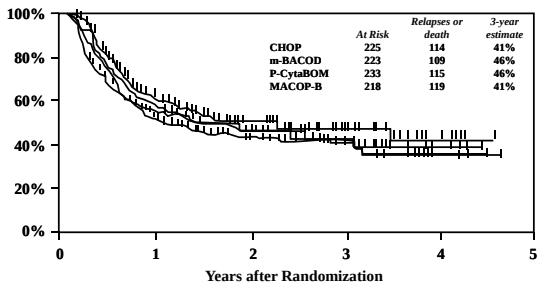
International Prognostic Index
Age-Adjusted (aaIPI)

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

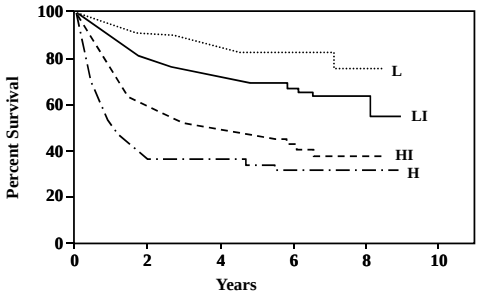
Shipp et al. *N Engl J Med.* 1993.

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



Fisher et al. *N Engl J Med.* 1993;328:1002.

International Prognostic Index
Age-Adjusted Overall Survival



*N Engl J Med.*1993;329:987.

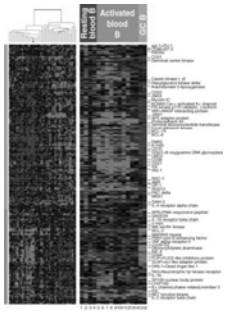
International Prognostic Index

Prognostic Indicators (APLES)
• Age > 60 years
• Performance status > 1
• LDH > 1 x normal
• Extranodal sites > 1
• Stage III or IV

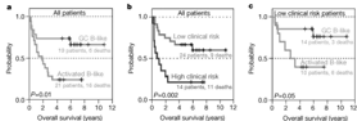
• Risk Category	Factors
• Low	0 or 1
• Low-intermediate	2
• High-intermediate	3
• High	4 or 5

Hiddemann. *E. J Cancer*. 1995; Jagannath et al. *J Clin Oncol.* 1986; Danieu et al. *Cancer Res.* 1986; Swan et al. *J Clin Oncol* 1989; Coiffier et al. *J Clin Oncol.* 1991; Shipp et al. *N Engl J Med.* 1993.

Diffuse Large B Cell Lymphoma
Distinct Forms Revealed by Expression Arrays

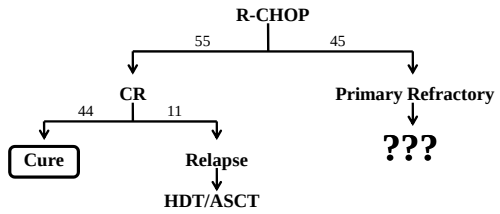


- Lymphochip expression array data segregates diffuse large B cell lymphoma into two molecular entities:
  - Germinal center phenotype
  - Activated B cell phenotype
- Molecular subtype is independent of International Prognostic Index risk group

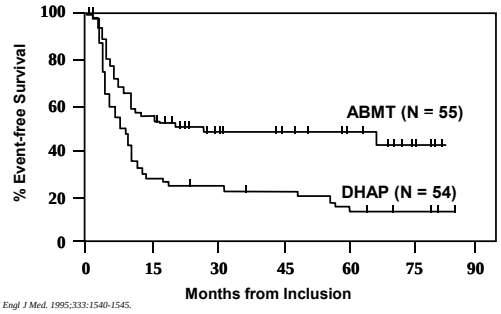


Alizadeh *et al. Nature* **403**:503-511 (2000)

Management of Aggressive NHL



Parma Trial: Event-free Survival



Philip et al. *N Engl J Med. 1995;333:1540-1545.*

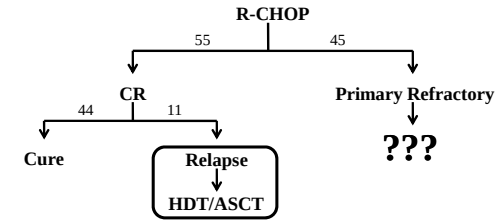
Aggressive Lymphoma

Second-line Therapy

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

Management of Aggressive NHL



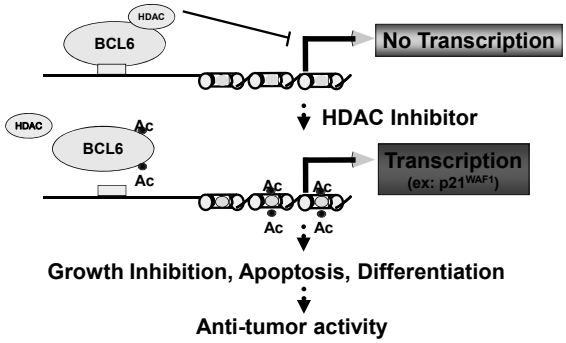
Therapy for Aggressive NHL
Summary

- R-CHOP remains the standard, albiet 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 (saaIPI) predicts survival
- Not all patients with relapsed and refractory aggressive NHL are potentially curable with this approach, particularly:
  - relapsed saaIPI IV
  - refractory saaIPI III/IV

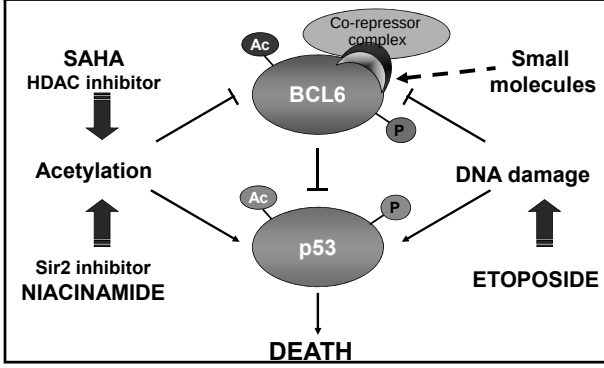
TARGETING BCL-6 IN LYMPHOMA



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 BCL6:p53 Network: A Rational Target



The Future of Cancer Therapy

Targeting the Molecular Pathways

Thank You