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Indolent Lymphomas

American Academy of Insurance Medicine 121st Annual Meeting

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Scottsdale, Arizona

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Jacksonville, Florida

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Objectives

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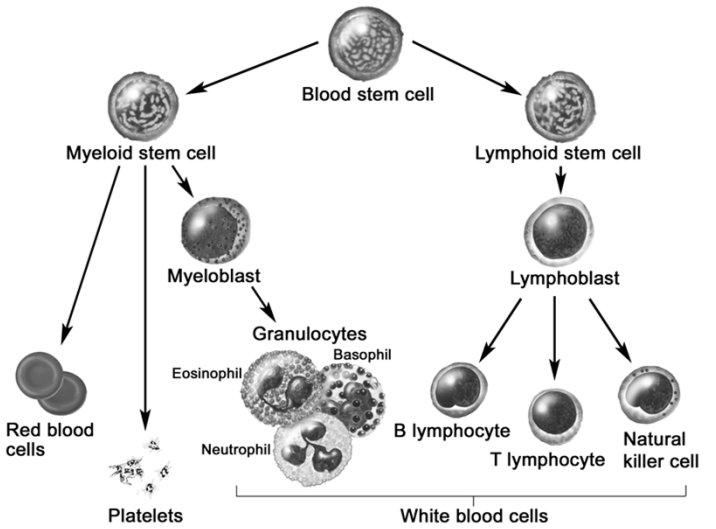
Blood Cells Develop from Stem Cells



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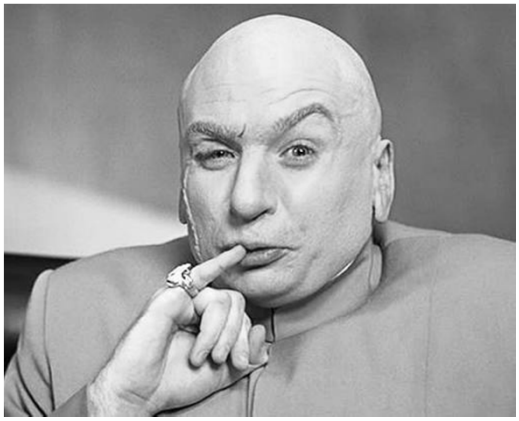
When Normal Hematopoiesis becomes Evil…



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Major Categories of Blood Cancers

Myeloid

Acute
- Acute Myeloid Leukemia

Chronic
- MPD
  - CML
  - PV
  - ET
  - PMF
- MDS

Lymphoid

Lymphoma
- Non-Hodgkins
- Hodgkins
- Overlap ALL

Chronic
- CLL
  - SLL
  - HCD
- LGL

Protein Diseases

Myeloma
- PCL
- Myeloma
- MGUS
- SM

Others
- Waldenstroms
- POEMS
- Amyloidosis

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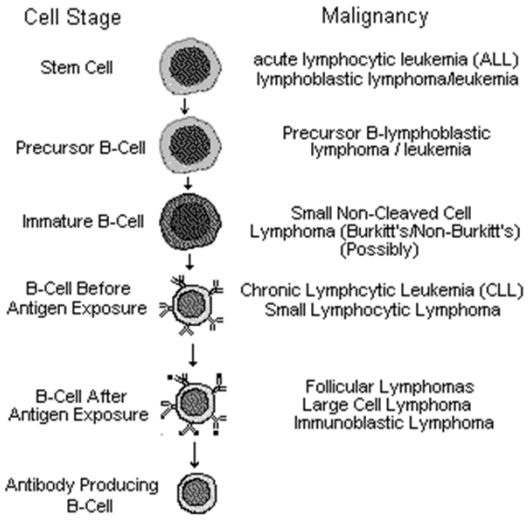
B Cell Cancers by Cell Development



Lymphoma Information Network
http://www.lymphomainfo.net/

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Myeloid Diseases

Acute → *Acute Myeloid Leukemia*

Chronic → *Myeloproliferative Disorders*

- Chronic Myeloid Leukemia
- Polycythemia Vera
- Essential Thrombocythemia
- Myelofibrosis

Chronic → *Myelodysplastic Syndromes*

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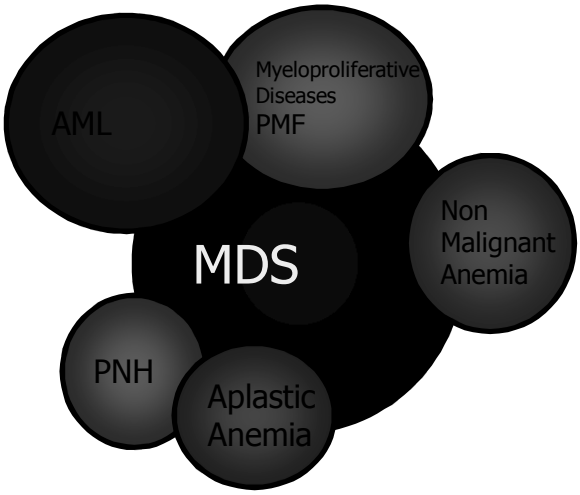
Overlapping Syndromes - Myeloid



Adapted from Young NS et al, Ann Intern Med. 2002;136:534.

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Lymphoid Diseases

Acute → *Acute Lymphoid Leukemia*
Aggressive Lymphomas

Chronic → *Lymphoproliferative Disorders*
Chronic Lymphocytic Leukemia
Non-Hodgkins Lymphoma
Hodgkins Disease

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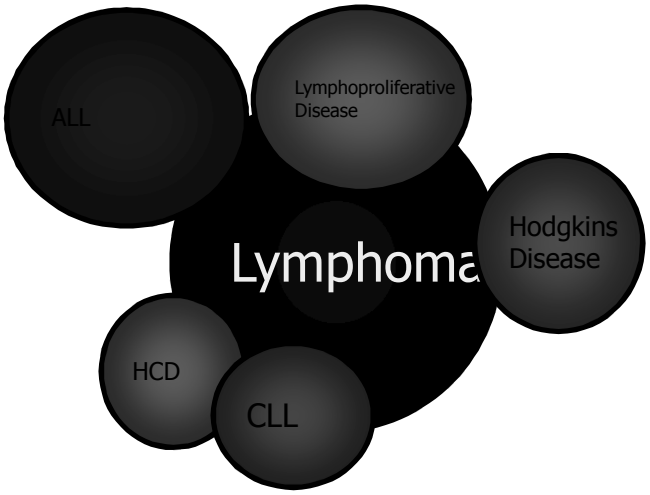
Overlapping Syndromes - Lymphoid



Adapted from Young NS et al, Ann Intern Med. 2002;136:534.

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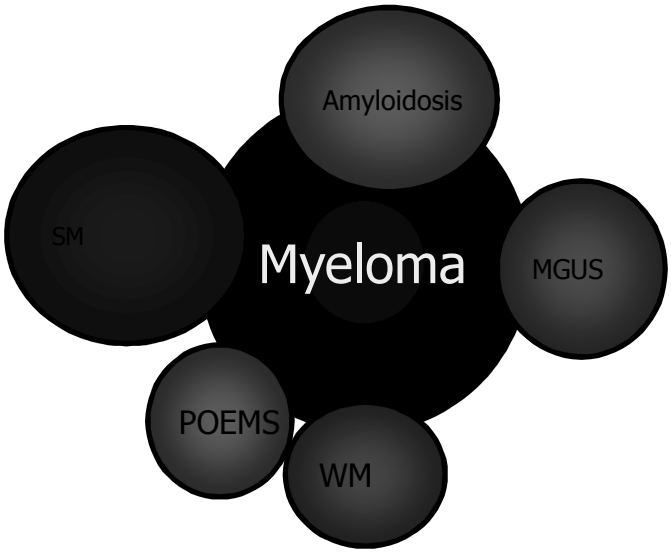
Overlapping Syndromes – Plasma Cell Disorders



Adapted from Young NS et al, Ann Intern Med. 2002;136:534.

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Non-Hodgkin's Lymphoma

Diverse group of malignant lymphoid tissue derived from progenitor T or B cells or mature T or B cells.

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Lymphoma Overview

- Lymphoma is the most common blood cancer
- More than 70,000 people are diagnosed each year
- Comprised of over 60 different subtypes of non-Hodgkin and Hodgkin lymphoma

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Epidemiology

- 5th most common cancer (after lung, prostate, colon & breast)
- On the rise?
  - Appears to be steady increase in incidence of lymphoma in both genders in major countries
  - Partial explanation for increase due to AIDS (8-27% of all cases)

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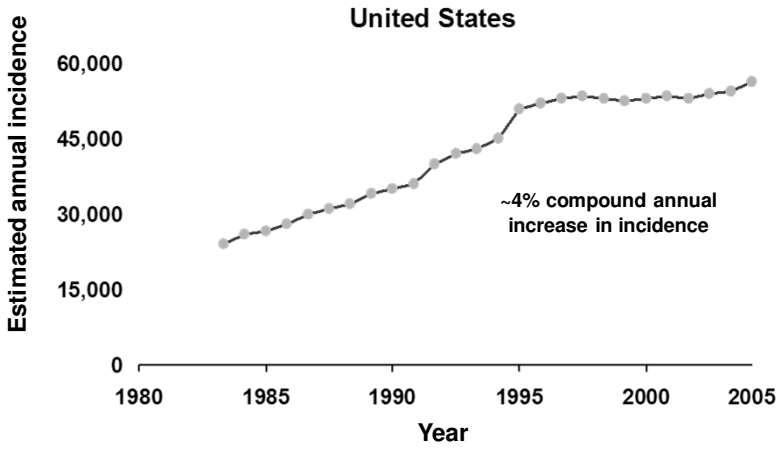
NHL Epidemiology



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Epidemiology

- Male to female ratio: 19.2 vs 12.2/100,000
- More common in whites
- Median age at diagnosis is 65
- Incidence increases with age
- Etiology not precisely known…

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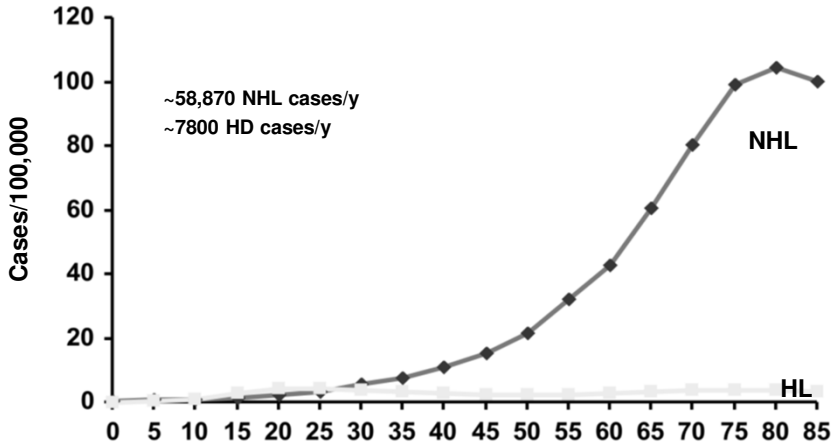
Age at Diagnosis



Data for diagnoses from 1997 to 2001.
Jemal et al. *CA Cancer J Clin.* 2006;56:106.
At: http://seer.cancer.gov. Accessed March 23, 2005.

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Risk Factors

- Immunodeficiency disorders
- Autoimmune disorders
- Organ transplantation
- Chemical or pesticide exposure
- Radiation exposure
- Bacteria or viruses

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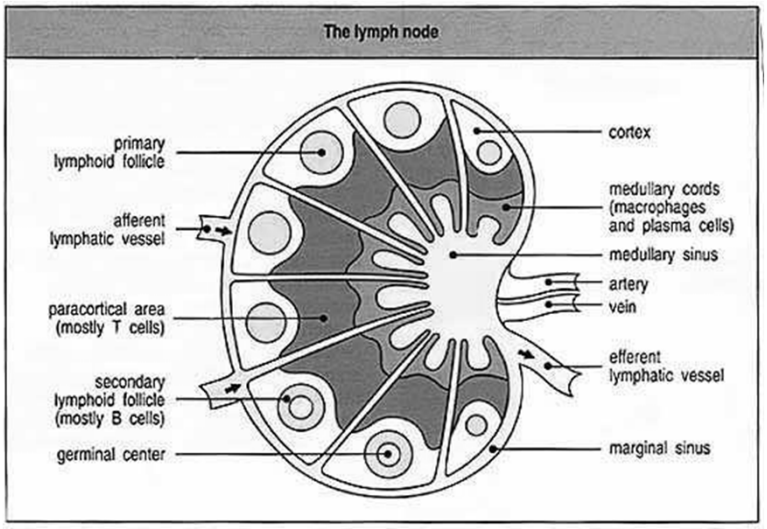

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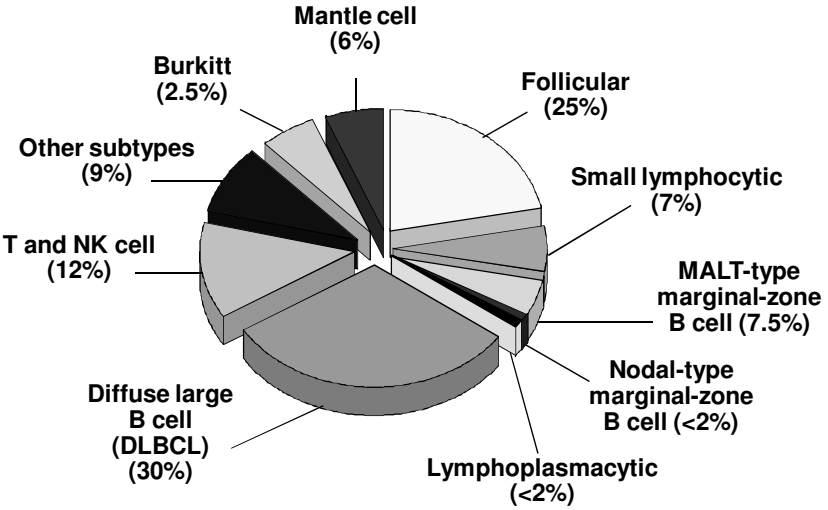
NHL Subtypes



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WHO Classifications for B-Cell Neoplasms

Indolent (Low Risk)	Aggressive (Intermediate Risk)	Very Aggressive (High Risk)
• CLL/SLL (IWF:A) • Lymphoplasmacytic leukemia • HCL • Splenic marginal zone lymphoma • Marginal zone Bcell lymphoma – Extranodal – Nodal • Follicular lymphoma, grades I-II (IWF:B-C)	• Follicular lymphoma, grade III (IWF:D) • PLL • Plasmacytoma/plasma cell myeloma • MCL • DLBCL – Mediastinal large B-cell lymphoma – Primary effusion lymphoma	• Precursor B-lymphoblastic lymphoma/leukemia • Burkitt's lymphoma/ Burkitt's cell leukemia

HCL=hairy cell leukemia; PLL=prolymphocytic leukemia; REAL=Revised European-American Lymphoma.

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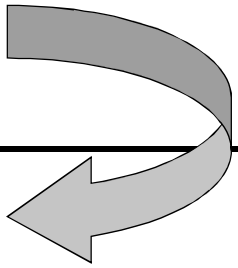
Clinical Course of NHL

- **Indolent (low grade)**
  - **Slowly progressive**
  - **Long natural history – "chronic disease"**
  - **Median survival: 6-10 years**
    - **5-year OS: up to 95%**
  - **Up to 50% risk of transformation**
  - **Treatable, but not curable**



- **Aggressive (intermediate grade)**
  - **Rapid clinical course**
    - **5-year OS: ~50%**
  - **Potential long-term survival with treatment**
- **Highly aggressive (high grade)**
  - **Grows rapidly**
  - **Survival: 0.5-2 years**
  - **Potential long-term survival with treatment**

Horning SJ. *Blood.* 1994;83:881-884.
Liu Q et al. *J Clin Oncol.* 2006;24:1582-1589.
Fisher RI et al. *N Engl J Med.* 1993;328:1002-1006.
Skarin AT, Dorfman DM. *CA Cancer J Clin.* 1997;47:351-372.

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SIMPLIFY…

- **Low Grade NHL: Survival is measured by years. Traditionally, considered incurable, with symptoms waxing and waning. Treat *ONLY* IF symptoms or bulky disease occur**
- **Aggressive NHL: Intermediate or high-grade disease. Survival is limited unless treated. *ALWAYS* treat even if no symptoms**

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Ann Arbor Staging

- **I: Single LN region or single extranodal site**
- **II: Two or more nodal regions same side of diaphragm**
- **III: Both sides of diaphragm (extra nodal or spleen)**
- **IV: Dissemination with or without nodal involvement**
- ***A* for asymptomatic & B for symptoms**
- ***E* for extra-nodal disease**
- ***X* for bulky disease and *S* for spleen involvement**

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Phenotypic Markers

Type	Positive	Karyotype	Oncogene	Function
CLL/SLL	CD5/CD23/CD20	Deletions	N/A	N/A
MCL	CD5/CD20	t(11;14)	Cyclin D1	Cell cycle regulator
FL	CD10/CD20/sIg	t(14;18)	BCL 2	Anti-apoptosis
MALT	CD20/CD11c/sIg	t(11;18) t(1;14)	MALT 1 BCL 10	Anti-apoptosis
DLCL	CD20/sIg	t(3;14) t(14;18)	BCL 6 BCL 2	Trans-Factor Anti-apop
BL	CD20/sIg	t(8;14) t(2;8) t(8;22)	cMYC	Trans-Factor

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IPI (International Prognostic Index)

- Age > 60 years
- LDH > Normal
- ECOG performance status (2-4)
- Stage III or IV
- Two or more extranodal sites
- If < 60 (LDH, PS, Stage)

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Effect on Survival

Risk Group	Risk Factors	CR (%)	OS (5 yrs)
Low	0 – 1	87	73%
Low-Inter	2	67	51%
High-Inter	3	55	43%
High	4 – 5	44	26%

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FLIPI
(for follicular lymphoma)

- **Age**
- **Stage (3 or 4)**
- **Hemoglobin (<120)**
- **LDH (elevated)**
- **> 4 nodal sites**

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The Follicular Lymphoma International Prognostic Index

Parameter	Adverse factor	RR	95% CI
Age	**≥ 60 y**	**2.38**	**2.04-2.78**
Ann Arbor stage	**III-IV**	**2.00**	**1.56-2.58**
Hemoglobin level	**< 120 g/L**	**1.55**	**1.30-1.88**
Serum LDH level	**> ULN**	**1.5**	**1.27-1.77**
Number of nodal sites	**> 4**	**1.39**	**1.18-1.64**

RR indicates relative risk (of death); CI, confidence interval; LDH, lactatedehydrogenase; and ULN, upper limit of normal.

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The Follicular Lymphoma International Prognostic Index

Risk Group	Number of factors*	Distribution of patients, %	5-year OS, % (SE)	10-year OS, % (SE)	RR	95% CI
Low	**0-1**	**36**	**90.6 (1.2)**	**70.7 (2.7)**	**1.0**	**NA**
Intermediate	**2**	**37**	**77.6 (1.6)**	**50.9 (2.7)**	**2.3**	**1.9-2.8**
High	**≥ 3**	**27**	**52.5 (2.3)**	**35.5 (2.8)**	**4.3**	**3.5-5.3**

N = 1795. OS indicates overall survival; SE, standard error; CI, confidence interval; RR, relative risk (of death), and NA, not applicable.

*Factors adversely affecting survival in the FLIPI include age greater than 60 years; Ann Arbor stage III-IV; number of nodal sites greater than 4; serum LDH level greater than the upper limit of normal; and hemoglobin level less than 120 g/L.

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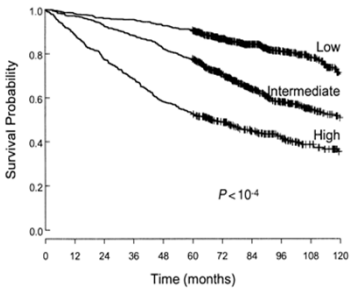
FLIPI



No. of Events											
Low	-	12	25	29	46	60	83	95	106	113	125
Intermediate	-	19	49	79	118	150	192	225	247	255	261
High	-	54	109	152	202	229	245	260	268	274	278
No. at Risk											
Low	641	629	616	612	595	581	450	337	241	157	93
Intermediate	670	651	621	591	552	519	385	263	178	108	68
High	484	430	375	332	282	255	193	139	98	56	33

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Criticisms of the FLIPI

- It is a compromise
- Many important factors not used
- May not agree with other indices
- Not all 5 prognostic factors have same relative risk
- Assumes that FL-3 behaves like FL-1 and FL-2
- Data come from the pre-rituximab era

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Non Hodgkin's Lymphoma
Clinical Presentation

- Vary greatly depending upon type (indolent vs. aggressive, B- vs. T-cell) and area of involvement
- "B" symptoms, various organ involvement and manifestations (skin, GI, CNS, organomegaly), cytopenias, lymphadenopathy.

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Diagnosis

- Physical examination
  - Lymphadenopathy
- Biopsy
  - Adequate tissue imperative
  - Excisional biopsy (optimal)
  - Multiple core biopsy may be acceptable
  - Fine needle aspiration is unacceptable
- Adequate immunophenotyping
  - Immunohistochemistry of paraffin sections
  - Flow cytometry to detect cell surface markers
- Cytogenetics/FISH to detect genetic abnormalities when appropriate

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NHL- Low grade/indolent

- Survival 8-10 years
- Incurable, but very treatable
- > 60% St III or IV
- Wax and wane, relapse
- 30% transform to higher grade (10yrs)
- Treat- when needed
- MoAb – 50-75% response

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Low Grade Lymphoma Treatment

- Limited stage (I, II) – 15%
  - *Radiation Therapy* - standard of care
  - Long term remissions – 50%
  - Impact on survival ?
  - Chemotherapy of no advantage
- Advanced stage - 85%
  - No curative therapy
  - Watch and wait if no sx's
  - Chemotherapy
  - Monoclonal antibody therapy

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Watchful Waiting

- "Watchful waiting" or "Watch and Wait"
  - Only for indolent low-grade NHLs
  - Regular physical exam and lab evaluation
  - No treatment until patient has:
    - Symptoms- fever, chills, night sweats, weight loss
    - Signs the disease is progressing
  - Spontaneous regressions have occurred
  - Treatment at diagnosis does not improve survival or decrease incidence of transformation to a more aggressive lymphoma
- This is NOT an option for aggressive lymphomas

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Treatment Options for Advanced Low-Grade Lymphoma

- Observation (watch and wait)
- Radiation
- Single-agent therapy
- Combination chemotherapy
- Interferon
- Monoclonal antibodies
- Hematopoietic transplantation
- Antisense molecules
- Vaccines
- Targeted agents

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Follicular Lymphoma: Indications for Therapy in Advanced Disease

- Cytopenias secondary to bone marrow infiltration
- Threatened end-organ function
- Symptoms attributable to disease
- Bulk at presentation
- Steady progression during > 6 mos of observation
- Presentation with concurrent histologic transformation
- Massive splenomegaly
- Patient preference
- Candidate for clinical trial

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Low Grade NHL – Chemotherapy

Single agent or combinations:

- Alkylating agents – cyclophosphamide, chlorambucil
- Vinca alkaloids – vincristine
- Bendamustine
- Corticosteroids – prednisone
- Purine nucleosides – Fludarabine, Cladribine
- Monoclonal antibody – Rituximab
- Conjugated MoAb – (RIT) Zevalin, Bexar

Combination:

- CVP
- CHOP
- FC
- Rituximab + chemo (R-CVP)

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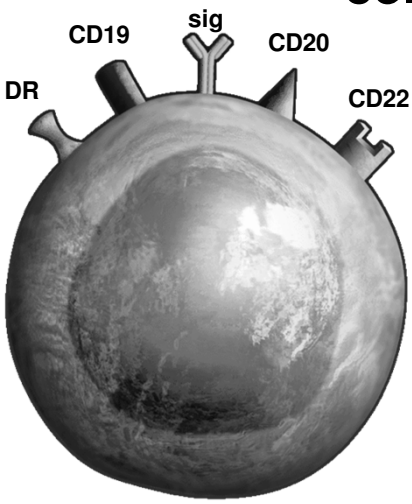
Immunotherapy Targets on B-cells



- Surface proteins targeted by immunotherapy
  - Naked monoclonal antibodies (mAbs)
  - Conjugated mAbs
    - Radioisotopes
    - Drugs
    - Toxins

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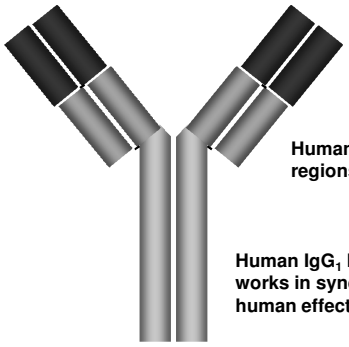
Rituximab



Murine/human IgG_1 kappa monoclonal antibody

Binds to CD20 antigen

Mechanism of action

- Complement-dependent cytotoxicity (CDC), Antibody-dependent cellular cytotoxicity (ADCC), cell death (apoptosis)

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Prolonged Survival With Chemo + Rituximab for FL

- **CVP vs R-CVP[1]**
- **CHOP vs R-CHOP[2]**
- **MCP vs R-MCP[3]**

Everything's better with Rituximab

1. Marcus R, et al. J Clin Oncol. 2008;26:4579-4586.
2. Hiddemann W, et al. Blood. 2005;106:3725-3732.
3. Herold M, et al. J Clin Oncol. 2007;25:1986-1992.

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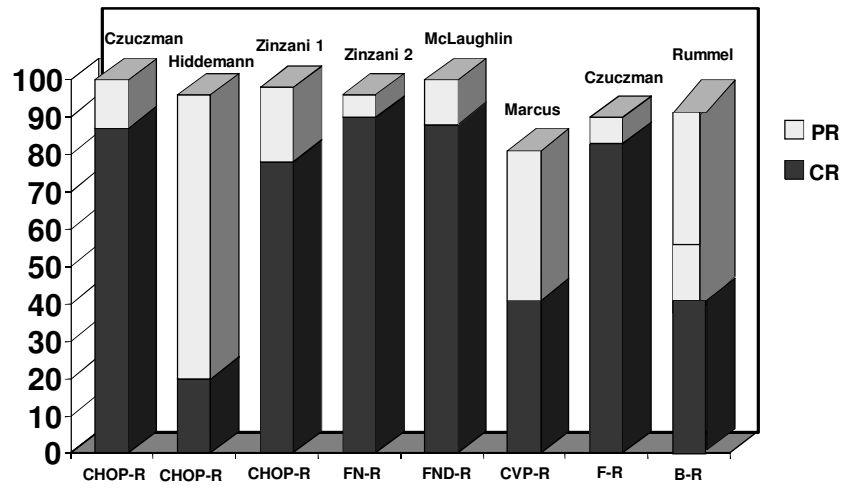
Chemo Rituximab Trials for Initial Therapy for Follicular NHL



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FDA Approved Agents

Agent	Indication
Rituximab (Rituxan)	•Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent •Previously untreated follicular, CD20-positive, B-cell NHL in combination with CVP chemotherapy •Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy •Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemo regimens •Front-line maintenance therapy in follicular lymphoma
Ibritumomab tiuxetan (Zevalin)	•Relapsed/refractory low-grade or follicular B-cell NHL •Previously untreated follicular NHL, who achieve a PR or CR to first-line chemotherapy
Tositumomab (Bexxar)	•Relapsed/refractory, low-grade or follicular B-cell NHL

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FDA Approved Agents contd.

Agent	Indication
Bendamustine (Treanda)	•Indolent B-cell NHL that has progressed during or within six months of receiving rituximab (Rituxan) or a rituximab-containing regimen •First-line and previously treated CLL
Bortezomib (Velcade)	**•Relapsed/refractory mantle cell lymphoma**

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Autologous Stem Cell Transplant in Lymphoma

- Relapsed Hodgkin lymphoma: Standard of Care
- Relapsed low grade lymphoma: Depends on patient, nature of relapse and other options
- Other: Relapsed Burkitt's lymphoma and relapsed lymphoblastic lymphoma
- Advantages
  - Readily available- patient is their own donor
  - No risk of graft-versus-host disease (GVHD)
- Disadvantages
  - Potential contamination with tumor cells requires collected marrow to be "purged"
  - No graft-versus-host tumor or graft-versus-leukemia effect

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Allogeneic Stem Cell Transplant in Lymphoma

- Not standard of care
- Often done after failure of an autologous stem cell transplant
- New technique referred to as
  - Nonmyeloablative transplantation
  - Mini-tranplant
- Advantages
  - No risk of tumor contamination
  - May produce additional anti-tumor effect
- Disadvantages
  - Locating a suitable donor
  - Risk of GVHD and graft rejection

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Novel Agents

- Incredible number of novel agents being developed, especially new MoAbs
- Over 40 in phase 2 and beyond…

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Conclusions

- Indolent lymphomas are common, incurable but well controlled in most patients
- Many do not have to be initially treated
- Median survival 8-10 years but growing
- Standard therapies include monoclonal antibodies +/- chemo
- Use of stem cell transplant waning with more novel agents available