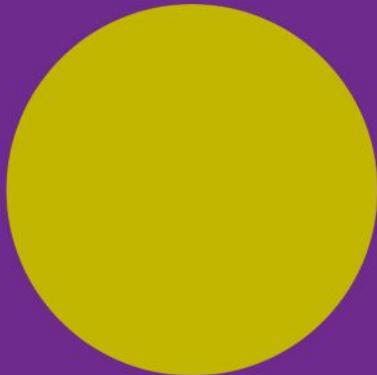


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Indolent Lymphomas

Dr. Melissa Toupin
The Ottawa Hospital



What does indolent mean?

- Slow growth
- Often asymptomatic
- Chronic disease with periods of relapse (long natural history possible)
- Incurable with current standard therapy, but long remissions possible
- Goal of treatment is to maximize quality of life



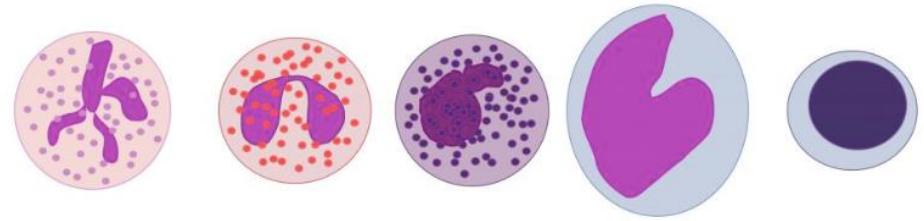
Indolent lymphomas (NHL)

	Incidence (per 100,000)
• Follicular	3.4
• Marginal zone or MALT	1.8
• Mycosis fungoides	0.4
• Waldenstrom's macroglobulinemia	0.3
• Hairy cell leukemia	0.3
• Primary cutaneous	0.1

SEER Database Incidence 2011-12



Lymphocytes



neutrophil eosinophil basophil monocyte lymphocyte

- **B cells** develop in the bone marrow
 - form antibodies against foreign bodies
 - 90% of all lymphomas
- **T cells** mature in the thymus gland
 - orchestrate the immune response
 - 10% of lymphomas
- **NK (natural killer) cells**
 - destroy viruses and cancers through direct attack
 - Very rare lymphomas, none indolent

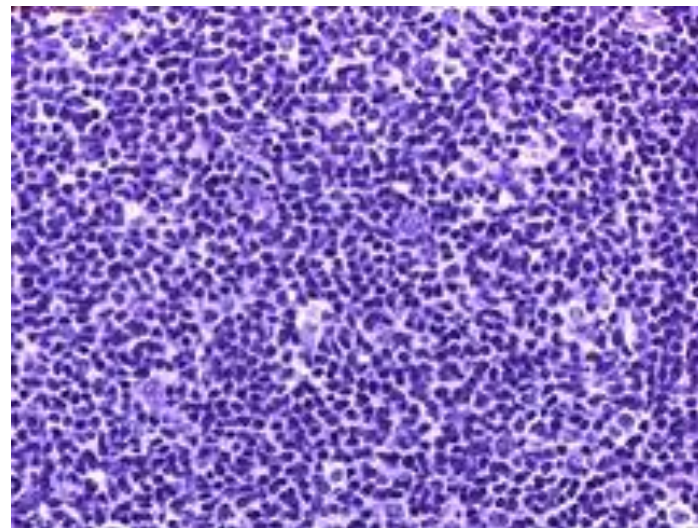
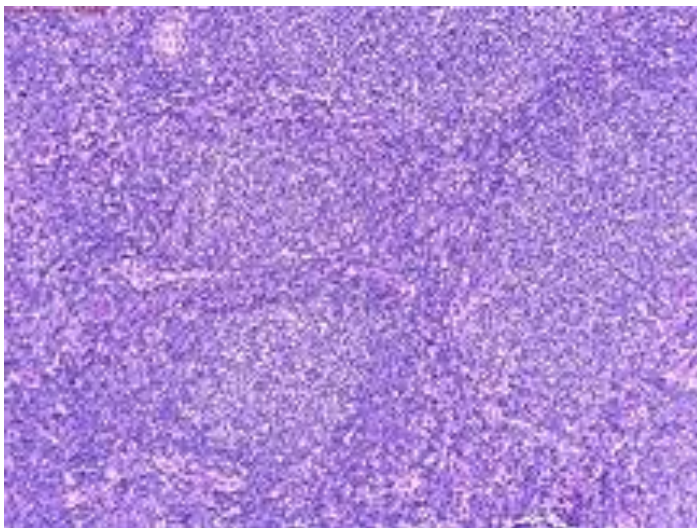


How do we figure out which type you have?

- **Physical Exam**
 - Lymph nodes, spleen
- **Biopsy**
 - Core needle biopsy
 - Excisional biopsy
- **Laboratory**
 - CBC and differential
 - LDH (prognostic marker in NHL)
 - Bone marrow aspirate/biopsy
- **Imaging**
 - CT scans
 - PET scan

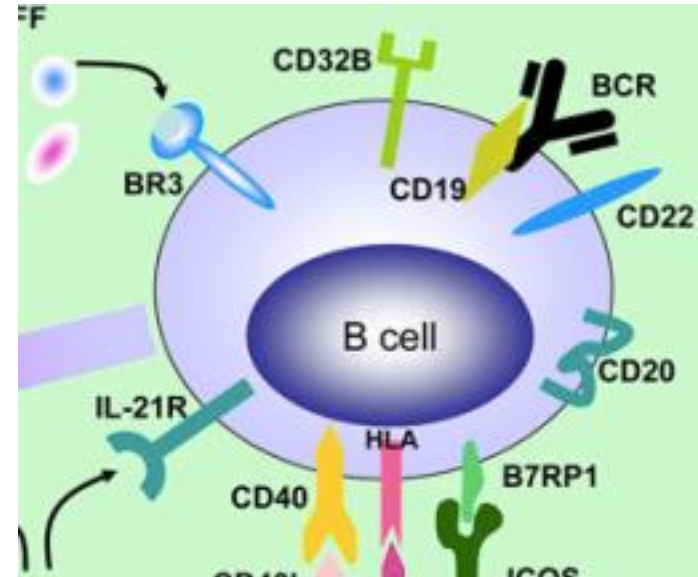


Biopsies



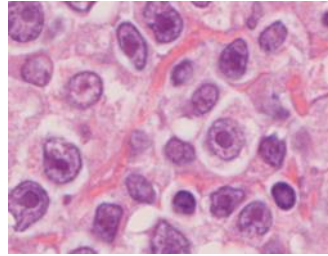
Why is pathology important?

- Need to determine the most appropriate therapy
- Some of the criteria for diagnosis are very specific—and lead to specific treatment choices:
 - CD20 “positive” by immunohistochemistry: use of rituximab

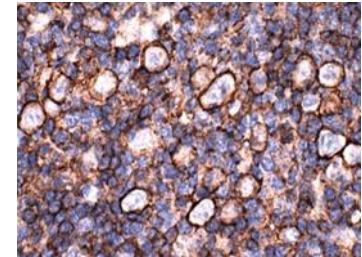


Pathology

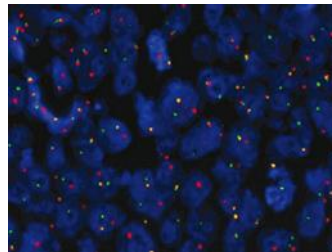
- Morphology



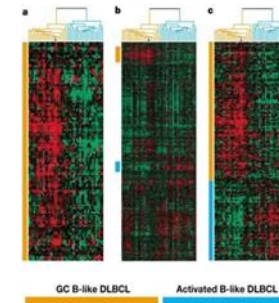
- Immunohistochemistry



- Cytogenetics



- Gene expression profiling



Staging

The # of staging investigations is dependent on the type of lymphoma and goals of therapy.

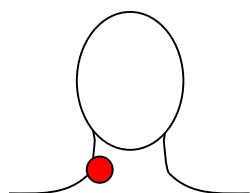
Staging is used to determine:

- Extent of disease
- Bulk of tumour mass
- Potential for complications
- Type of treatment

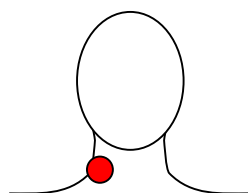


Ann Arbor Staging System

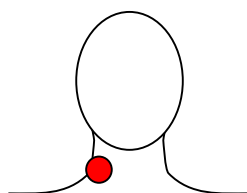
Stage I



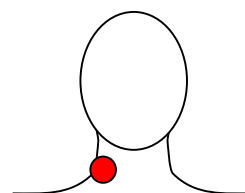
Stage II



Stage III

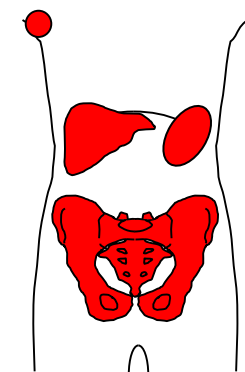
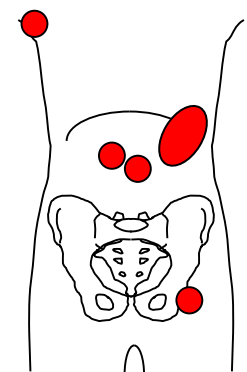
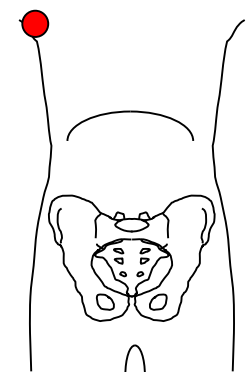
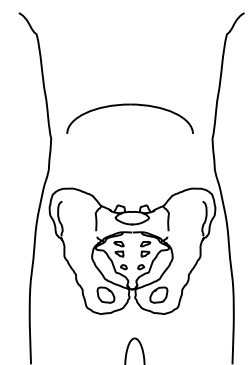


Stage IV



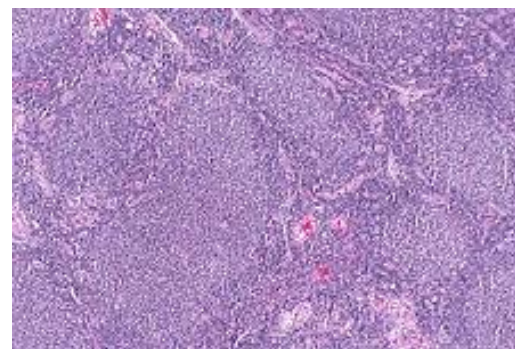
A – absence of any “B” symptoms

B – Unexplained fever, drenching sweats or weight loss



Follicular lymphoma

- Typically affects middle-aged and older adults
- Abnormal follicles give disease its name
- Causes few symptoms in early stages
- Usually responds well to treatment, but can return
- Can transform into aggressive lymphoma



FLIPI- 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	1.50	1.27-1.77
Number of nodal sites	> 4	1.39	1.18-1.64

Score	Prognosis	% Patients	OS (10 yr)
0-1	good	36	71
2	moderate	37	51
3-5	poor	27	36



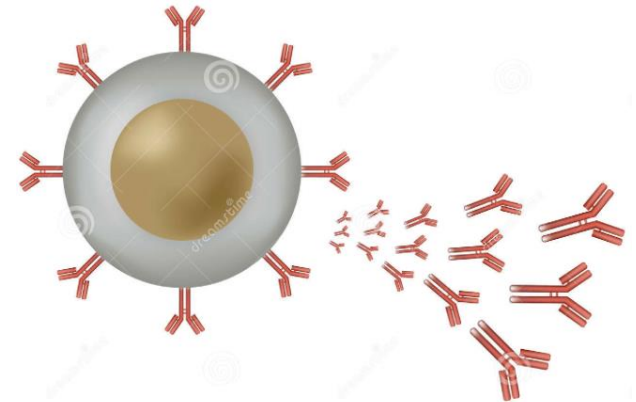
Marginal zone lymphoma

- Accounts for ~10% of NHL
- Affects older adults usually
- 3 types:
 - **Extranodal marginal zone lymphoma or mucosa-associated lymphoid tissue (MALT)**
 - Occurs outside the lymph nodes in the stomach, small intestine, salivary glands, thyroid, eyes or lungs
 - **Nodal marginal zone lymphoma**
 - Occurs within lymph nodes
 - **Splenic marginal zone lymphoma**
 - Usually occurs in spleen and blood



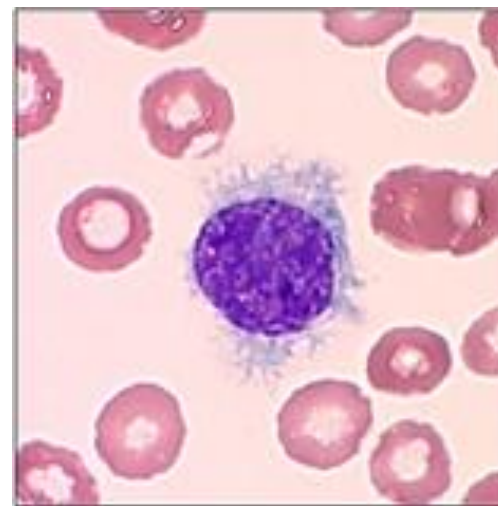
Waldenstrom's macroglobulinemia

- Dr. Jan Waldenstrom first described the condition in 1948
- Rare, 1-2% of NHLs, usually affecting older adults
- Primarily found in bone marrow
- Overproduction of IgM protein, causing thickening of blood
- Plasmapheresis may temporarily reverse or prevent symptoms associated with blood thickening.



Hairy cell leukemia

- Surface of cells look hairy under microscope
- Called 'leukemia' as cancerous lymphocytes can be found in the blood, though they mainly collect in the bone marrow and spleen
- Rare subtype usually found in middle-aged or older adults



Cutaneous lymphoma



- Lymphoma in the skin
- Usually T cell, but can be B cell
- Most common subtype: mycosis fungoides
- Most common in those aged 50+, but can occur in younger adults
- Often small, raised, red patches on skin that may look like eczema or psoriasis
- Ulcerating tumours (open sores) can appear
- Treatment may include ultraviolet light



Watch & wait

Randomized trial of “Watch and Wait” vs. early chemotherapy
British National Lymphoma Investigation Trial of 309 patients with indolent NHL

Results	“Watch and Wait”	Early chemotherapy
Lymphoma-specific survival	No difference	
Overall Survival	No difference	

- On average, patients needed treatment ~2.5 years from diagnosis
- However, 1 in 5 participants did not require treatment by 10 years
- 2 in 5 over the age of 70 did not require treatment



Coping with watch & wait

- Be gentle with yourself
- Talk it out
- Take care of yourself (healthy living)
- Learn about lymphoma (dispelling the myths)
- Ask for support



Indications for starting treatment

- Symptoms attributable to the lymphoma
- Low blood counts because of bone marrow involvement
- Threat to organ function
- Bulky disease or spleen
- Disease that has transformed to an aggressive lymphoma



Overview of primary treatment options

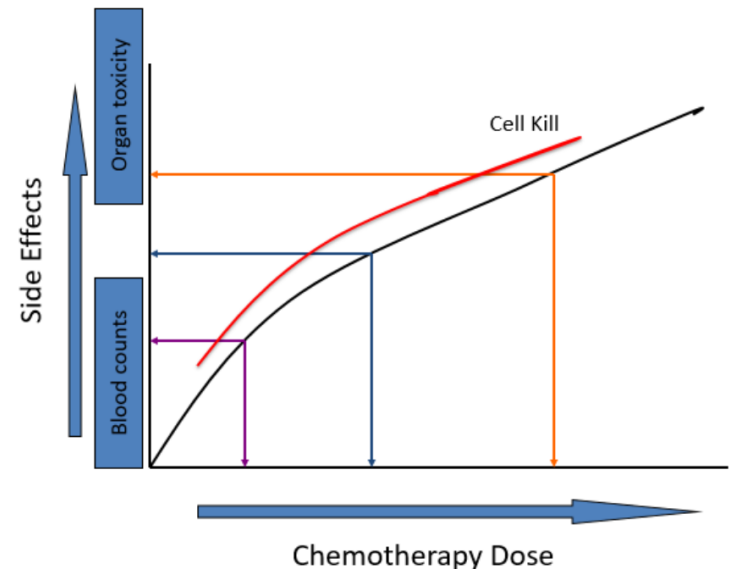
Treatment Option	Description
Chemotherapy	Use of drugs to kill lymphoma cells
Radiation Therapy	Use of high-energy rays to kill lymphoma cells or slow their growth
Immunotherapy	Use of agents designed to target and destroy lymphoma cells
Transplantation	Infusion of healthy stem cells/bone marrow to help the body restore its supply of healthy blood cells

Balance potential toxicity against effectiveness



Chemotherapy

- Backbone of many cancer treatments
- Damages DNA, leading to cell death
- Systemic
- Affects all growing cells
 - Cancer cells
 - Blood cells
 - Lining of GI tract
 - Hair



Common chemotherapy regimens

Bendamustine – with R (Rituximab)

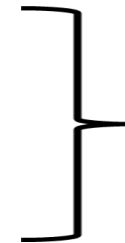
- IV, days 1 and 2, 28-day cycles
- Usually 6 cycles total
- In Ontario – since 2013
- Progression-free survival ~70 months
- Side effects:
 - No hair loss
 - Nausea/vomiting
 - Suppression of immune system
 - Rashes, constipation/diarrhea



Common chemotherapy regimens

CHOP - with or without R (Rituximab)

- ✓ Cyclophosphamide
- ✓ Doxorubicin
- ✓ Vincristine
- ✓ Prednisone— pills daily x 5 days



By IV every
3 weeks

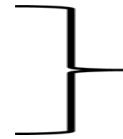
Usually 6 cycles



Common chemotherapy regimens

CVP – with or without R (Rituximab)

- Cyclophosphamide
- Vincristine
- Prednisone — pills daily x 5 days



By IV every
3 weeks

Usually 6 cycles

Even more gentle option = rituximab alone



Immunotherapy

- Also called biologic therapy
- Drugs designed to boost the body's natural defenses against cancer
- Generally fewer side effects than traditional chemotherapy

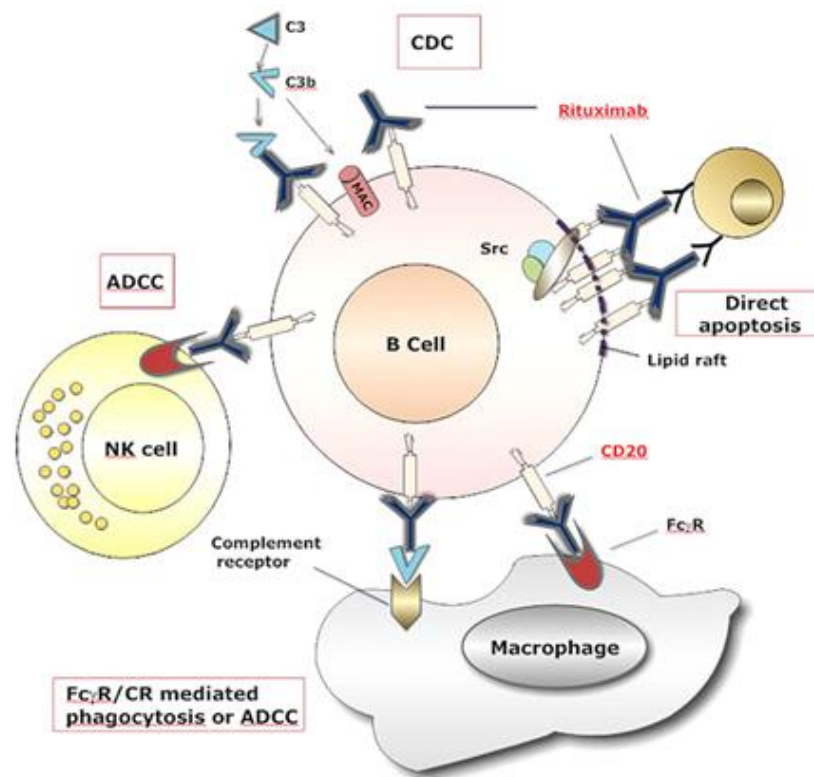


Monoclonal antibodies

Antibodies developed against cancer cells can be administered to patients to destroy the tumour

- Examples:
 - Rituximab
 - Obinutuzumab

Only work for B cell lymphomas



Samantha M. Jaglowski et al. Blood 2010;116:3705-3714



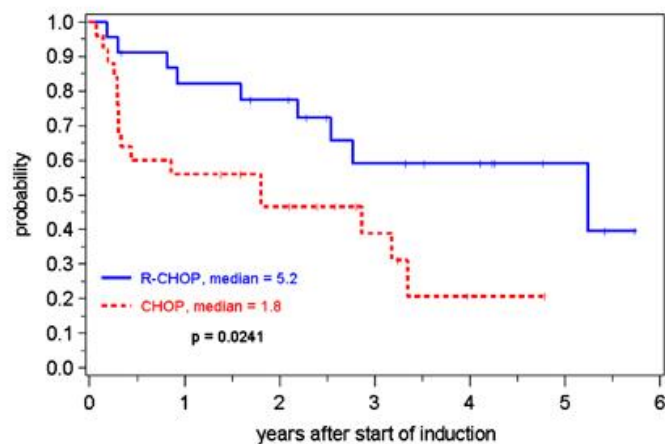
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Why add rituximab?

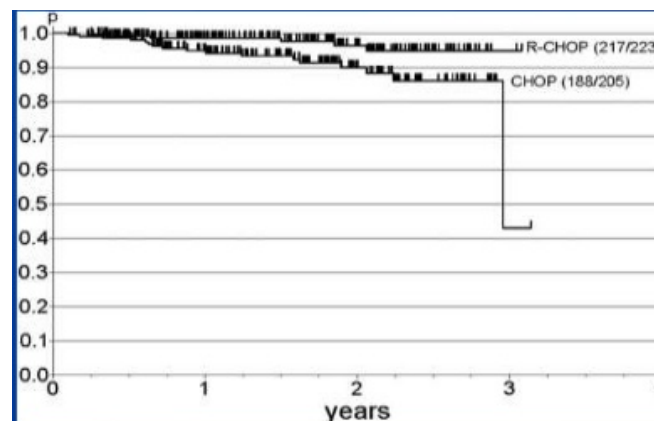
Addition of anti-CD20 antibody rituximab to chemotherapy: improvement in survival.



numbers of patients at risk

R-CHOP	23	18	16	9	7	3	0
CHOP	25	14	10	5	1	0	

Waldenstrom's Macroglobulinemia CHOP vs R-CHOP, German Low Grade Lymphoma Study Group, Phase III Trial Results



Follicular Lymphoma CHOP vs R-CHOP, Hiddemann et al, 2005



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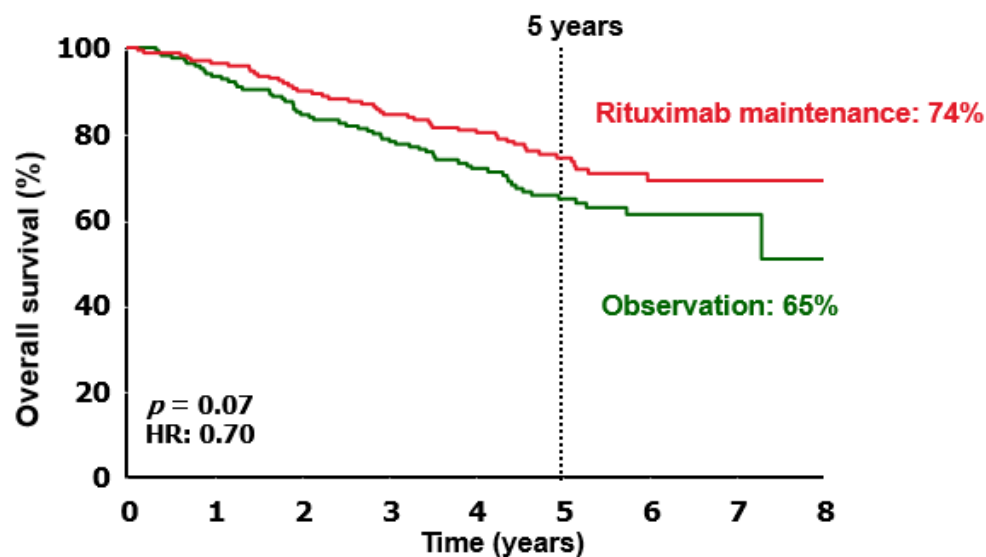


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Rituximab maintenance

- Rituximab maintenance for 2 years
- Administered every 3 months, 8 cycles

FL



van Oers MHJ, et al. *J Clin Oncol* 2010; 28:2853–2858.



Targeted therapies

Drugs that target specific molecules on the surface of cancer cells or cell pathways.

Bortezomib

Ibrutinib

- Pill, taken as directed until disease progression or intolerance to drug develops



Radiation

Medical uses of radiation:

1. **Diagnostic:** low doses of radiation to take images of internal body structure i.e. chest x-ray
2. **Therapeutic:** higher doses of radiation to kill cancer cells

Difference between the two is the amount of energy. Therapeutic radiation can use up to 1,000 times the energy of diagnostic radiation.



Radiation

- X-ray beams interact with atoms, creating a reaction that leads to cell DNA damage
- Damage prevents the cells from dividing and growing
- Lymphocytes are the most sensitive cells in the body to radiation, so can use lower doses of radiation compared to what is used to treat solid tumours.



Radiation



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Radiation

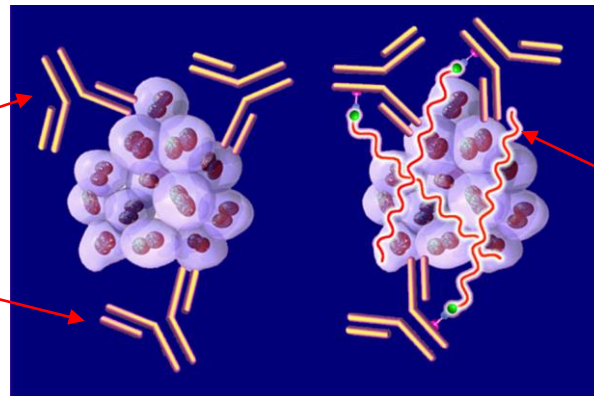
- Applies to localized disease, or for palliative purposes (to relieve symptoms)
- May not be used in all types of indolent NHL
- Generally treatment is given daily for 4 weeks (Monday to Friday X 4 weeks = 20 treatments or “fractions”)
- Side effects based on the area that is being radiated (skin and tissue beneath it)



Combination therapy

- Chemotherapy + radiation
- Chemotherapy + immunotherapy = chemoimmunotherapy
- Radiation (radioactive isotopes) + immunotherapy = radioimmunotherapy

Monoclonal antibody alone



With radioactive isotopes



Side effects of treatment

Short term:

- Hair loss
- Mouth sores
- Nausea, vomiting: controllable with medication
- Fatigue
- Fever: need a thermometer! If ≥ 38.3 get a blood test (even Sunday afternoon...)
- Low blood counts



Other possible issues

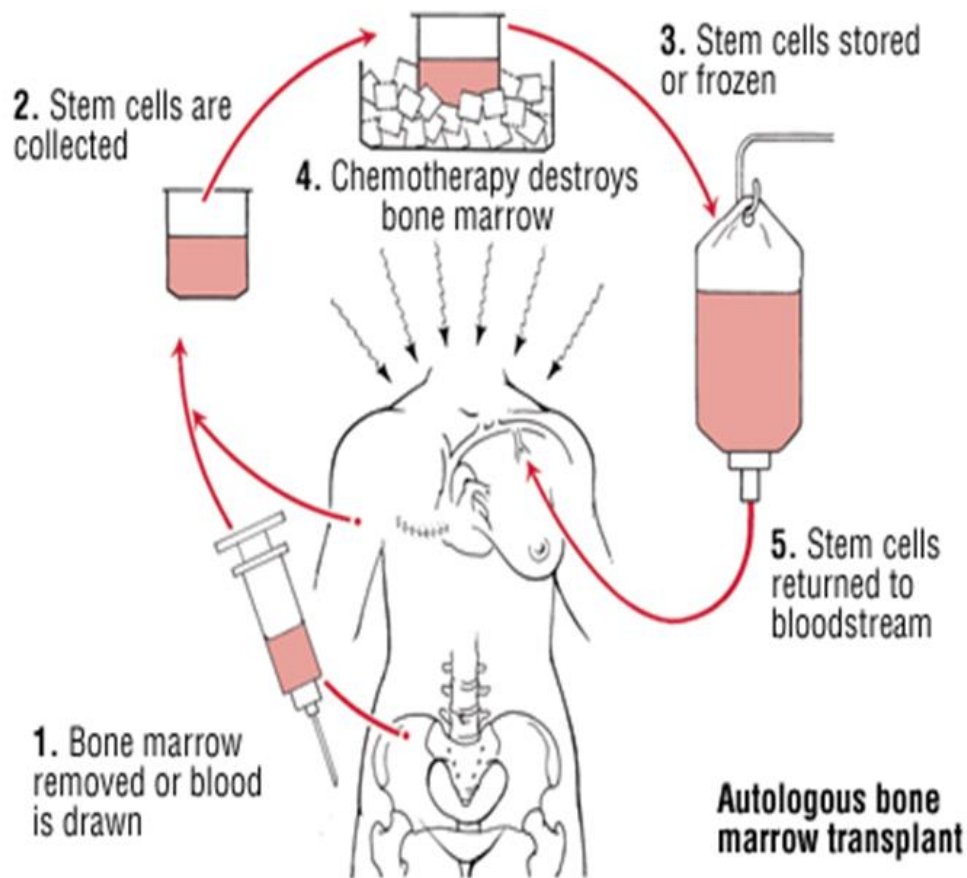
- Heart function: may need monitoring
- Peripheral neuropathy (numb hands, feet)
- Difficulty with memory, concentration (multi-tasking)– “chemobrain”
- Fertility



Stem cell transplant (SCT)

Autologous

- Use own cells
- Low treatment related mortality
- High rates of remission
- Transplant strategies vary centre-to-centre



Stem cell transplant (SCT)

Allogeneic

- Rare
- HLA matched sibling or matched unrelated donor
- 1 in 4 chance of sibling being a match
- Graft versus lymphoma: good!
- Graft versus host disease: can be very bad, including fatal, and life long
- Higher treatment related mortality



After treatment is completed

- Repeat staging tests to determine if the lymphoma is “in remission”
 - Hope that we have attained a long period of disease control before we have to re-treat the lymphoma
- Follow-up with your family MD (~annually)
 - Screening for secondary cancers
 - Vaccines
- Follow-up with your oncologist (~3 months)

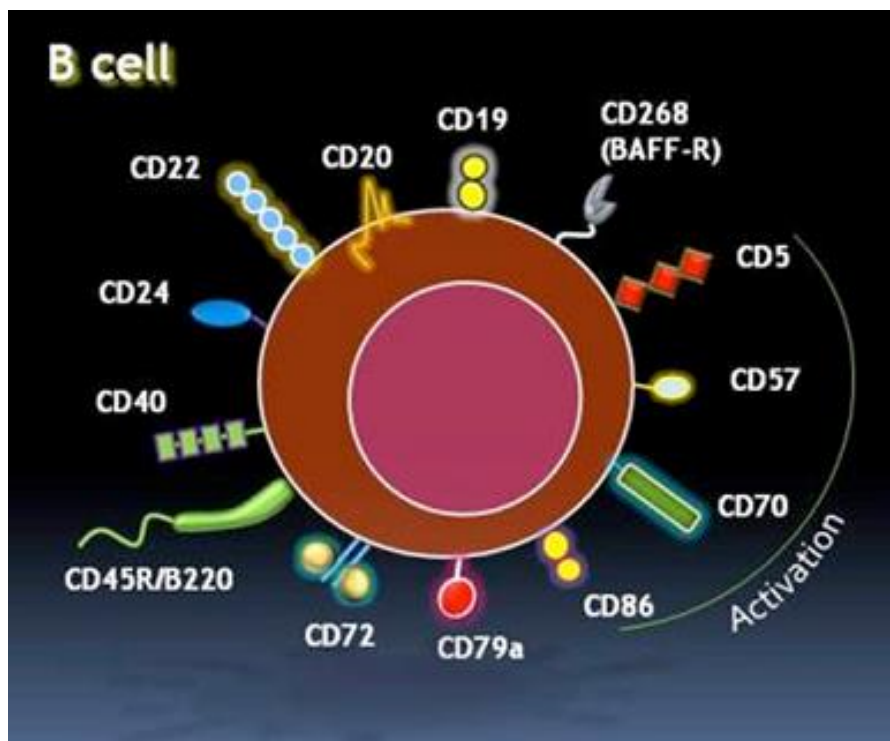


Relapse/refractory

- Many other treatments available
- Goals of therapy may change
- Clarification of goals with your oncologist is very important
- Clinical trials of new agents



Cell surface targets



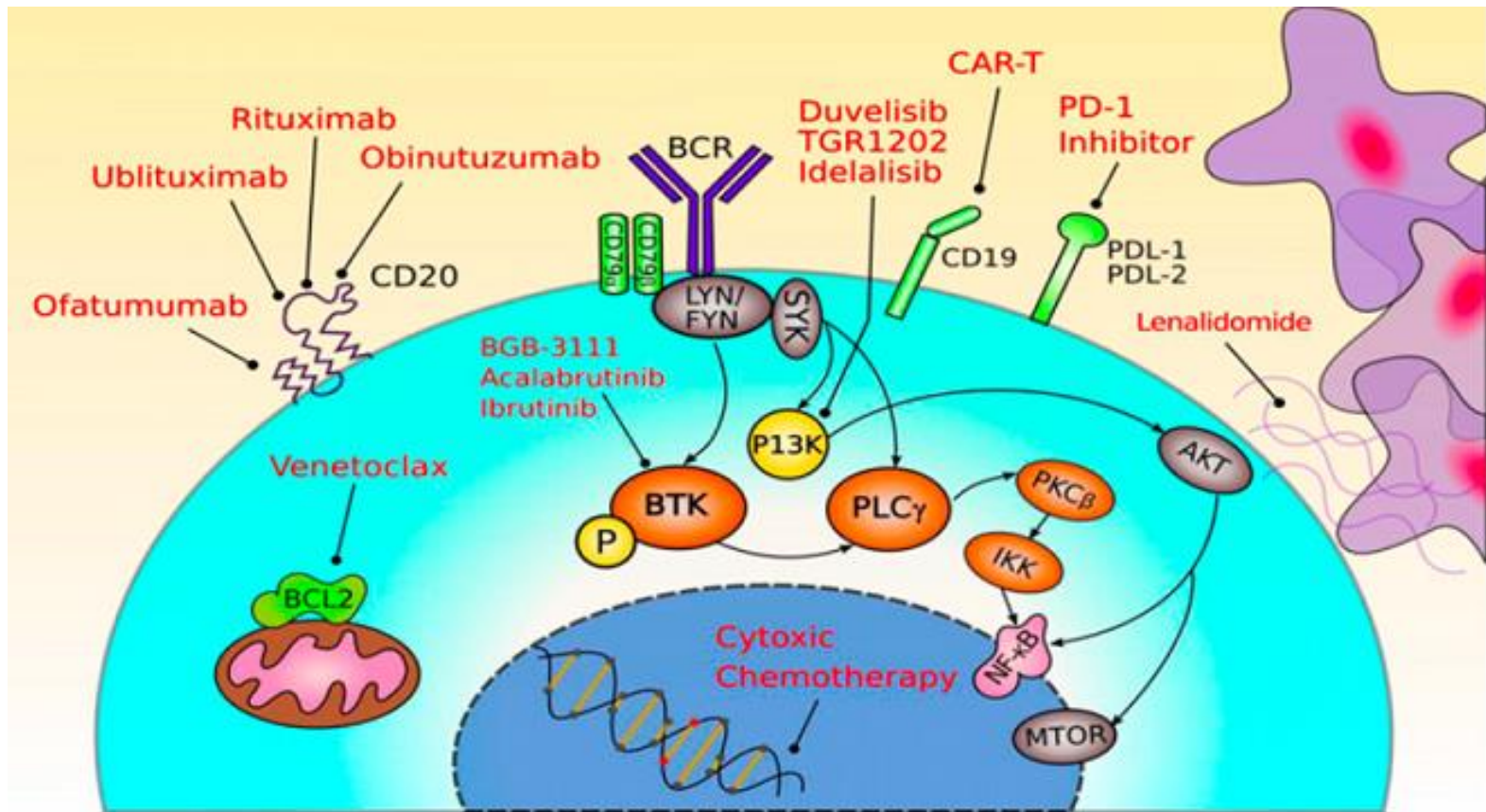
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