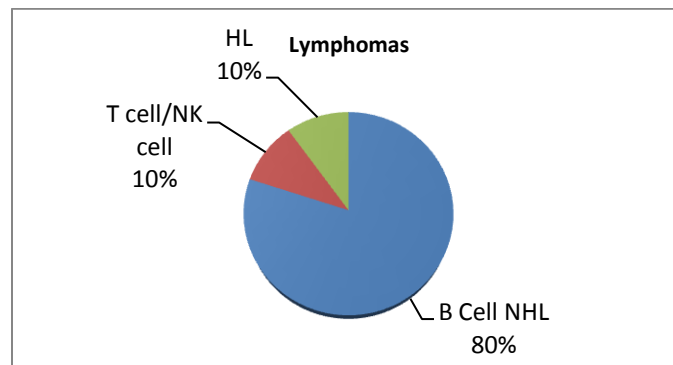


NON- HODGKIN'S LYMPHOMA (NHL)

LYMPHOMAS

GENERAL

- One of the most curable and treatable malignancy
- Diverse group of disorders
- Lymphoma biology and management has led to several major breakthroughs in cancer treatments
- Lymphoma incidence is increasing
- About 79,000 new cases with 20,000 deaths from lymphoma in 2013 per ACS estimate
-



NON-HODGKIN'S LYMPHOMA (NHL)

GENERAL

- NHL comprises of heterogeneous group of disorders with variable clinical presentation, therapy, prognosis and clinical course.
- Incidence is increasing
- Disease spread is generally non-contiguous

INCIDENCE

- In United states of America:
 - About 69,700 cases annually (2013 estimate)
 - About 19000 deaths annually (2013 estimate)

RISK FACTORS and ETIOLOGY

- Etiology is unknown for most cases
- Suspected but not conclusively proven: Pesticides, Chemicals, Smoking, Hair dyes, toxins
- Immuno compromised states increase risk of NHL
 - Drug treatments: Cyclosporine, OKT 3 in transplant patients, etc.
 - Infections: HIV
 - Inherited immune defects
 - Collagen vascular diseases: Rheumatoid arthritis

- Stem cell transplantation or solid organ transplantation
- Association between infectious agent and specific type of lymphoma: See table below

Association between infectious agent and specific type of lymphoma		
Epstein Barr virus	Hodgkin's lymphoma Post transplant lympho-proliferative disorders (PTLD)	
Human Herpes virus 8	Body cavity lymphoma Castleman disease HIV related Kaposi's sarcoma	
Hepatitis C virus	Immunocytoma Splenic marginal zone lymphoma	
Human T cell Lymphoma virus	Adult T cell leukemia/lymphoma	
Helicobacter pylori	Gastric mucosa associated lymphoid tissue lymphoma (MALTOMA)	
Chlamydia Psitacci	Orbital adnexal lymphoma	
Campylobacter jejuni	Immunoproliferative small bowel disease	
Borrelia burgdorferi	Cutaneous MALT lymphoma	

PATHOGENESIS

- Many genetic alterations are reported in NHL (See each subtype for details)

PREVENTION STRATEGY

- Unknown

SCREENING

- Not available

SYMPTOMS / SIGNS

- Pain less lymphadenopathy
- Splenomegaly
- B symptoms: Fever, drenching night seats, weight loss, pruritus

DIAGNOSIS

- Requires biopsy:
- Excisional node biopsy is preferred for histology and flow cytometry
- FNA has high false negative rate and can not differentiate between nodular versus diffuse subtypes or T cell rich B cell NHL
- Core biopsy may be sufficient to document relapse of previously diagnosed NHL
- Distant sites or bone marrow aspiration and biopsy may give diagnosis
- Flow cytometry and molecular genetic studies are increasingly useful in diagnosis

HISTOLOGY

- Long succession of Various classifications
- WHO modification of REAL (Revised European American Lymphoma) classification is in use currently and accepted universally:

- REAL classifications: See textbook for details.

STAGING SYSTEM

NHL often presents at advanced stage. Ann Arbor staging system is less relevant for NHL than for HL.

Ann Arbor staging

- Stage I: Involvement of single lymph node region or lymphoid structure
- Stage II: Involvement of two or more lymph node regions confined to same side of diaphragm
- Stage III: Involvement of two or more lymph node regions on both sides of diaphragm
- Stage IV: Disseminated disease (marrow, liver etc)
- Substages:
 - A: Absence of B symptoms;
 - B: Presence of B symptoms (fever over 37°C on two occasions not related to infection, unintended loss of more than 10% body weight within six months, drenching night sweats)
 - E: Extra nodal site involvement by direct extension of a node

STAGING WORK UP AND OTHER TESTING

- History and physical examination
- Excisional lymph node biopsy with histology and immune phenotype (Flow cytometry)
- CBC diff, Liver enzyme testing, LDH
- CT chest, CT abdomen and pelvis are necessary for staging.
- PET scan:
 - Identifies more disease sites than CT. However may or may not alter stage in 75%. Stage may change in 25% but treatment may not change in all.
 - May help absence of distant disease in stage I patients who may be candidate for RT only.
 - PET is useful in assessing response for diffuse large cell lymphoma (A CR by PET may translate to potential cure).
 - PET is less sensitive for marginal zone lymphoma or small lymphocytic lymphoma or peripheral T cell lymphoma.
- Bone marrow aspiration and biopsy is necessary for staging.
- Fertility preservation evaluation if applicable
- Pulmonary function testing
- Cardiac ejection fraction tests
- HIV testing
- Vaccination if splenectomy is planned or splenic RT is given

CLINICAL DECISION MAKING AND ESTIMATION OF PROGNOSIS:

- Clinical categorization of each case into one of the following categories might help in clinical decision making.
 - Indolent lymphoma: (Slow growing, low grade, incurable)
 - Aggressive lymphoma: (fast growing, intermediate grade, potentially curable)
 - Highly aggressive (high grade, very fast growing, potentially curable)

INDOLENT LYMPHOMAS

- Follicular lymphoma is most common Indolent lymphoma.
- Generally considered slow growing and are considered incurable
- In general there is no consensus on best treatment. Many options are available including observation.
- Prolonged survival is typical in Indolent lymphoma.
- Indolent lymphoma generally include:
 - Follicular grades I and II
 - Marginal Zone lymphoma
 - Lympho-plasmacytic lymphoma (Immunocytoma and Waldenstorm’s Macroglobulinemia)
 - Small lymphocytic lymphoma

PROGNOSTIC GROUPS BASED ON FLIPI:

- Follicular lymphoma International Prognostic Index (FLIPI) based on
 - Age over 60 years
 - Stage III or IV disease
 - LDH level
 - Hemoglobin level
 - Number of extra nodal sites

Follicular lymphoma : Overall Survival based on FLIPI				
Risk group	# of risk factors	5 yr overall survival	10 yr overall survival	
Low	0-1	90.6	70.7	
Intermediate	3	77.8	50.9	
High	3-5	52.5	35.5	

- Age (≤ 60 y vs. >60 y).
- Serum lactate dehydrogenase (LDH) (normal vs. elevated).
- Stage (stage I or stage II vs. stage III or stage IV).
- Hemoglobin level (≥ 120 g/L vs. <120 g/L).
- Number of nodal areas (≤ 4 vs. >4).

FOLLICULAR LYMPHOMA (Grade 1 and 2)

- About 20% of total NHL and 70% of all indolent lymphoma
- Characterized by follicular growth pattern on biopsy
- CD 20 positive, CD 10 positive, CD 5 negative, CD 23 negative.
- BCL-2 is over expressed in 85% or more {as a result of t (14, 18) (q32, q 21)} – can be detected by FISH or PCR. BCL 2 is considered to be responsible for immortality of NHL cells
- BCL – 6 is positive as well
- Early stage follicular lymphoma
 - About 10-15% Follicular lymphoma patients have stage I or non bulky stage II disease – potentially curable
 - Involved field RT produces 10 year FFS of 50-60% and OS of 60-80%
 - Observation till symptomatic disease progression is also an option – long term survival is possible
- Advanced stage follicular lymphoma
 - About 85-90% patients with Follicular lymphoma have advanced disease (bulky stage II, stage III or stage IV) at presentation
 - Overall survival is still up to 10 years

- Remember: Despite long clinical course, Follicular lymphoma is considered incurable.
- Early treatment of advanced disease does not prolong survival
- Watch and wait is conventional approach till symptoms develop
- Indications for treatment may include:
 - Increasing adenopathy
 - Disease related symptoms
 - Organ compromise
 - Marrow failure and cytopenias
- Treatment options
 - Many options are available. Optimal treatment regimen is unknown and there is no consensus
 - Antibody treatments
 - Many antibodies and radio immunoconjugates are available
 - CD 20 is most targeted antigen. Rituximab is most used anti-CD 20 antibody - Monotherapy RR: 50-70%
 - Median duration of response is 1-2.5 years
 - Maintenance Rituximab: for up to 2 years prolong time to progression and event free survival
 - Rituximab is well tolerated. General side effects are fever and chills during infusion, cytokine release syndrome which could be fatal – patient with high number of circulating cancer cells are at risk, delayed neutropenia may occur.
 - Combination of chemotherapy + Rituximab (CVP-R or CHOP-R or Fludarabine-Rituxan or Bendamustine – Rituxan)
 - Favorable progression free survival and event free survival
 - Doxorubicin based therapy is generally reserved for refractory state
- Relapsed follicular lymphoma;
 - Relapses are common
 - Salvage therapy depends on prior treatment, quality of prior response, performance status, organ function and marrow involvement
 - Rituximab may prolong PFS
 - No evidence exists so far that more aggressive salvage regimens are any better
 - New agents: Bendamustine, Bortezomib and Lenalidomide
 - Radio-immunotherapy is an option for some – high responses in some trials – reserved for patients with less than 25% marrow involvement because of myelotoxicity
 - Stem cell transplant is controversial
- Transformation to aggressive lymphoma
 - About 30-40% follicular lymphoma transform to higher grade typically diffuse large cell B cell lymphoma
 - Annual rate is about 3%
 - Rapid growth of single nodal area may occur
 - R-CHOP is appropriate treatment but cure rates are low about 10% (much less than de novo Diffuse large cell B cell lymphoma)
 - Median survival is 6-20 months after transformation
 - Stem cell transplant is suggested for healthy patients – 20-30% long term survival after transplant

Treatment options for Follicular and low grade NHL	
Watchful waiting	
Anti CD 20 antibody – Rituximab	
Oral alkylators (Chlorambucil, Cyclophosphamide)	
Purine analogues (Fludarabine, Cladarabine, Pentostatin)	
Combination chemotherapy (CVP-R, CHOP-R, FCR, B-R)	
Radio-immuno conjugates	

Stem cell transplantation	
Experimental vaccines or oligonucleotides	

MARGINAL ZONE LYMPHOMA

- Behaves like other low grade indolent lymphomas
- Trisomy 3 and t(11,18) are seen in up to 60% cases
- t(11,18) produces a fusion protein called MALT1 which impairs apoptosis and favors cell proliferation
- Most present with stage I or II
- Can be seen in marrow or nodes or blood or spleen
- Nodal marginal zone lymphoma is treated similar to Follicular lymphoma.
- Splenic marginal zone lymphoma :
 - Splenic marginal zone lymphoma presents with massive splenomegaly and blood and marrow involvement but no adenopathy. Splenectomy may result in prolonged remission and symptom control. Also responds well to chemotherapy regimens similar to CLL – Rituximab, Fludarabine or combinations. Hepatitis C treatment may induce remission of lymphoma in some patients
- MALT lymphoma:
 - Extra nodal marginal zone lymphoma (Mucosa associated lymphoid tissue – MALT) may involve GI tract, thyroid, lung, breast or skin: May have auto immune disorders (Hashimoto's thyroiditis, Sjogren's syndrome).
 - Stomach MALTOMA are associated with H. Pylori – treatment with triple regimen may induce MALTOMA remission in 60%– radiation or Rituximab or chemotherapy are reserved for patients not responding to H. Pylori treatments. Cases with t(11, 18) translocation appear to be resistant to triple antibiotics.
 - Immunoproliferative small bowel disease or small intestinal MALTOMA or heavy chain disease is seen in young adults (specially from middle east) and responds to antibiotics treating *Campylobacter jejuni*

SMALL LYMPHOCYTIC LYMPHOMA (SLL)

- Abnormal accumulation of mature lymphocytes with CD 5 positive, CD 20 positive and CD 23 positive
- Clinical course , treatment and prognosis are similar to CLL

WALDENSTORM'S MACROGLOBULINEMIA / Lympho-plasmacytic lymphoma

- Generally associated with monoclonal IgM protein
- Marrow, nodal and splenic involvement is common
- PAX 5 gene rearrangement is seen in about 50% {associated with t(9, 14)}
- Complicated by neuropathy, amyloidosis, cryoglobulinemia and cold agglutinin disease
- Mixed cryoglobulinemia is associated with hepatitis C in many
- Hyperviscosity syndrome can be seen in about 30% (if viscosity goes over 4)
 - Retinopathy, CHF and mental status changes may occur
 - Plasmapheresis is useful in acute symptoms
- Rituximab or chemotherapy can produce prolonged remissions
- Hepatitis C treatment may induce remission of lymphoma in occasional patients
- General treatment is similar to Indolent follicular lymphoma
- Cure is unlikely
- Median survival is 5-10 years

- Large cell NHL transformation occurs in about 24%

MANTLE CELL LYMPHOMA (MCL)

- Characterized by CD 5 positive, CD 20 positive mantle cells (similar to CLL cells which are also CD 5 and CD 20 positive) , however, containing t (11,14) translocation and over expression of BCL 1 – cycling D1 protein)
- Negative for CD 23 and CD 10
- May have diffuse bowel involvement (lymphomatous polyposis)
- Median survival is shorter than other lymphomas
- Doxorubicin based chemotherapy may not cure MCL – initial responses are common but do not last long - durable responses are not common
- Refractory disease is common
- Long term remissions are uncommon
- Hyper CVAD followed by High dose therapy and stem cell transplantation in first CR is considered better option and is recommended in fit patients
- Bortezomib is approved for recurrent and refractory disease

BURKITT LYMPHOMA

- Highly aggressive lymphoma with explosive presentation
- Starry sky pattern on histology
- All cases possess c-Myc oncogene at band 8q24 {associated with t (8,14) mostly but sometimes with t(2,8) or t (8, 22) }
- Common in pediatric population (Endemic in Africa – jaw tumors and associated with EBV)
- Most common lymphoma in AIDS patients
- Non endemic Burkitt's is seen in US
 - GI tract (ileo-cecal mass) is commonly involved and LDH is very high
 - Very intensive treatment regimen (R-hyper CVD or R-CODOX-M/IVAC) and CNS prophylaxis may cure some patients (60% -74% DFS at 5 years in adults)
 - Rituximab added to chemotherapy increases response rates
 - Responses are high 85-95%
 - Fatal tumor lysis is possibility – precautions are necessary
 - Stem cell transplantation is recommended for those in first CR with high risk of recurrence (Stages III or IV, high LDH and tumor masses more than 10 cm)

PRIMARY CNS LYMPHOMA

- Aggressive B cell lymphoma in cranio-spinal axis without systemic disease
- Seen De novo or in immuno compromised patients
- Age over 60 and HIV are poor prognosticators
- Whole brain RT is standard but unsatisfactory treatment
- CHOP does not work well
- RT with or without chemotherapy is neuro toxic
- Radiation sparing regimens: Chemotherapy alone with high dose Methotrexate and Leucovorin rescues is being tried with better response than RT. Recurrences are common within 2-3 years and RT can be deferred for recurrent lymphoma.
- Rituximab or Temozolamide is being tried in salvage setting.

LYMPHOBLASTIC LYMPHOMA

- Seen in young adults
- T cell gene rearrangements are common
- Tdt positive
- Highly aggressive lymphoma of precursor T or B cells
- Explosive onset: Commonly with blasts in blood, marrow, mediastinal and other adenopathy, younger age, cytopenia. About 30% experience CNS involvement
- Induction therapy: Intensive multi-agent chemotherapy in hospital setting. Hyper CVAD results in 90% CR in low risk patients
- Consolidation: Stem cell transplantation
- CNS prophylaxis and radiation to bulky tumor are important components of treatment
- Testis and CNS are sanctuary sites
- Testicular RT is incorporated in treatment protocols
- Relapses are rare after 1 year
- High risk cases can rapidly relapse – 5 year survival is less than 20%
- Poor prognosticators: Older age, BCR-ABLE gene – t (9, 22), MLL gene- t (4, 11) or del 7 or trisomy 8.
- About 40% may be disease free after intensive treatment
- Clinical course , treatment and prognosis are similar to ALL

DIFFUSE LARGE CELL B CELL LYMPHOMA (DLBCL)

- Most common NHL – 30% -35% of total
- B cells are positive for CD 19 and CD 20
- Most present with rapidly developing masses, systemic symptoms or weight loss
- IPI is used to estimate prognosis and to classify patient in to risk groups: Derived from patient database from Pre-Rituximab era.
- Aggressive B cell lymphoma International Prognostic Index (IPI)
 - Age : Under or over 60 years
 - Stage: I - II versus III - IV disease
 - Serum LDH level: normal or increased
 - Performance status – 0-1 versus 2-4
 - Number of extra nodal sites: 0-1 versus more than 1
 -

Aggressive B cell lymphoma International prognostic index (IPI)				
Risk group	# of risk factors	CR rate %	2 yr RFS survival	5 yr RFS survival
Low	0-1	87	79	70
Low-Intermediate	2	67	66	50
High-intermediate	3	55	59	49
High	4-5	44	58	40

- DNA micro array based distinct sub groups may provide better prognostic information – needs to be validated in prospective studies
- Localized DLBCL: about 20% cases
 - Stage I or non bulky stage II
 - Potentially Curable

- R-CHOP x 3 with Radiation is used commonly in USA after SWOG trial
- RT alone may not be adequate – high rate of relapse
- GELA study reported no benefit of RT added to chemotherapy but results are questioned because of poorer survival in all early stages
- Advanced DBCL
 - CHOP alone- 50-70% CR and plateau at DFS at around 30%
 - R-CHOP versus CHOP: R-CHOP improved CR, TTP and overall survival in GELA study – several other trials confirmed benefit of R-CHOP. Addition of Rituximab to CHOP was major therapeutic advance after decades of stagnation (Rituximab improves cure rate by about 10-15%)
 - R-CHOP is current standard of care for DBCL
 - More than half can be cured with R-CHOP
- Relapsed DBCL
 - Re-induction with aggressive chemotherapy regimen such as RICE – remission occur in 50-70% but are of short duration and few are cured
 - Consolidation stem cell transplantation may cure some relapsed patients – long term DFS in 40-50% patients with chemo-sensitive disease
 - Stem cell transplant is less effective for primary refractory disease – allogeneic transplant is being studied
- Repeat biopsy may help since 10-15% may have lower grade follicular recurrence

HAIRY CELL LEUKEMIA

- Seen in older males
- Splenomegaly, Leukopenia / pancytopenia and marrow infiltration with hairy cells (cytoplasm projections)
- TRAP positive cells
- Marrow is fibrotic and hard to aspirate (Dry tap is common)
- Purine analogues (Cladarabine or Pentostatin) are effective in inducing prolonged remission lasting for up to 8-12 years
- Splenectomy, Rituximab, Anti CD22 antibody are used as salvage
- Cure is not expected like other indolent lymphomas

POST TRANSPLANT LYMPHO-PROLIFERATIVE DISORDERS (PTLD)

- Seen in solid organ transplant patients requiring lifelong immuno suppressive therapy
- Associated with Epstein Barr virus
- Monoclonal or polyclonal forms of lymphoma may occur
- Withdrawal of immuno suppressive therapy may induce remission in some
- Rituximab may help – in about 60% patients
- Acyclovir and Interferon have been tried
- R-CHOP is reserved for refractory cases
- Localized disease can be treated with Radiation

PERIPHERAL T CELL LYMPHOMA – PTCL

- Diverse group of post thymic T cell (mature T cell) tumors
- Most have advanced disease and B symptoms
- Prognosis is considered poor
- CHOP type aggressive regimens are used but responses are lower with few long term remission

- Relapses are common
- Angio-immunoblastic T cell lymphoma
 - Generalized adenopathy, weight loss, rash, positive coomb’s test and hyper gamma globulinemia
 - Complicated by serious infections
- Extra nodal NK/T cell lymphomas
 - Seen in Asian patients with nasal masses and EBV positive tumors
 - RT + chemotherapy is used with poor responses

CUTANEOUS T CELL LYMPHOMA – CTCL (Mycosis Fungoides)

- Indolent T cell (helper cell CD 4 phenotype) lymphoma of skin
- Waxing and waning eczematous skin patches or plaques for long periods (5-15 years)
- Advanced disease: Nodular tumors with ulceration or systemic visceral involvement
- Treatment options are many including PUVA (Psoralen and ultraviolet A therapy), local radiation, retinoids, interferon, Denilukin –IL2 fusion toxin, topical chemotherapy or purine analogues or liposomal doxorubicin or Vorinostat)
- Patient can die from infections – good skin care and antibiotics are important components
- Sezary syndrome: Generalized erythema and circulating Sezary cells in blood – median survival is short – about 2 years with Sezary syndrome
- The only curative therapy is allogeneic stem cell transplant – option for a small number of patients

SPECIAL SITUATIONS

- B cell SLL and CLL are different expressions of same neoplasm
- Lymphoblastic lymphoma and ALL represent same clinical entity
- Comparisons of major types of NHL

Indolent NHL	Aggressive NHL
Slow growth	Rapid growth
No or few symptoms	Symptoms
Age over 40 years	Any age
Advanced stage	Early or advanced stage
Incurable mostly	Potentially curable

FOLLOW UP

- Purpose of long term follow up:
 - To monitor for relapse
 - To monitor for late effects of treatment
 - To monitor for new primary cancer
- Late effects of treatment
 - Myelo-dysplasia
 - Treatment related secondary leukemia
- Secondary cancers
 - In long term survivors

PROGNOSIS

- Overall prognosis is worse than Hodgkin's lymphoma
- See above under treatment section

SAMPLE QUESTIONS