

MALIGNANT LYMPHOMAS

General Consideration

- Lymphomas are malignant transformation of lymphoid cell which reside predominantly in lymphoid tissues.
- Counterparts of the normal lymphoid cells at varying stages of differentiation & development.
- Morphologically, they are small round blue cell tumors

- Lymphoproliferative classification
 - Hodgkin's Lymphoma (HL)
 - Non-Hodgkin's lymphoma (NHL)
- The natural course, prognosis and therapeutic approach depends on
 - Type of lymphoma
 - Stage
- Accurate diagnosis and staging is essential

Classification

- Multiple classification systems in history
 - Rappaport
 - Kiel
 - Lukes-Collins
 - Working Formulation
 - Revised European-American classification of Lymphoid Neoplasms (REAL)
- Newer classification (WHO)
 - Understanding of
 - Immunology
 - Molecular biology
 - Basically list of 20+ malignancies under
 - B-, T- & NK- Cells

- HL

- Not put under this classification
- Excellent prognosis
- Classified by its own (histologically)
 - Classical
 - Lymphocyte Predominant
 - Lymphocyte-Depleted
 - Nodular Sclerosis
 - Mixed Cellularity
 - Non-Classical
 - Nodular Lymphocyte-Predominant

- Clinical relevance
 - Based on the clinical behavior of NHL specially
 - Not part of WHO classification system
- Classification according to the clinical relevance
 - HL
 - NHL
 - INDOLENT
 - AGGRESSIVE
 - HIGHLY AGGRESSIVE

The indolent lymphomas

B-cell neoplasms

Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia

Lymphoplasmacytic lymphoma ($\pm$ Waldenstrom's macroglobulinemia)

Plasma cell myeloma/plasmacytoma

Hairy cell leukemia

Follicular lymphoma (grade I and II)

Marginal zone B-cell lymphoma

Mantle cell lymphoma

T-cell neoplasms

T-cell large granular lymphocyte leukemia

Mycosis fungoides

T-cell prolymphocytic leukemia

Natural killer cell neoplasms

Natural killer cell large granular lymphocyte leukemia

The aggressive lymphomas

B-cell neoplasms

Follicular lymphoma (grade III)

Diffuse large B-cell lymphoma

Mantle cell lymphoma

T-cell neoplasms

Peripheral T-cell lymphoma

Anaplastic large cell lymphoma, T/null cell

The highly aggressive lymphomas

B-cell neoplasms

Burkitt's lymphoma

Precursor B lymphoblastic leukemia/lymphoma

T-cell neoplasms

Adult T-cell lymphoma/leukemia

Precursor T lymphoblastic leukemia/lymphoma

Definition of NHL classes

- **INDOLENT**

- Survival of untreated disease measured in years
- Even CR does not lead to a cure
- Not curable with conventional treatment

- **AGGRESSIVE**

- Survival of untreated disease measured in months
- CR required for cure
- Curable with conventional treatment

- **HIGHLY AGGRESSIVE**

- Survival of untreated disease measured in weeks
- CR required for cure
- Curable with conventional treatment

C			
CHARACTERISTICS	HL	INDOLENT NHL	AGGRESSIVE NHL
SITE OF ORIGIN	Nodal	Nodal (E-10%)	Nodal (E-35%)
NODAL DISTRIBUTION	Centripetal	Centrifugal	Centrifugal
NODAL SPREAD	Contiguous	Noncontiguous	Noncontiguous
LOCALIZED PRESENTATION	Common	Rare	Rare to common
GI PRESENTATION	Rare	Common	Common
BM INVOLVEMENT IN PROGNOSIS	Yes	No	No
B-SYMPTOMS	Common	Rare	Rare
IMMUNITY PREDOMINANTLY AFFECTED	cellular	humoral	C or h

DDX OF LYMPHOMAS

- Infectious agents with prominent LAP
 - Viral (CMV, IM, HIV, HHV8)
 - Secondary syphilis
 - Mycobacteria
 - Fungal
 - toxoplasmosis
- Systemic Immune Disorders- RA, SLE, Sarcoidosis
- Head & Neck tumors and other malignancies with secondary to the LN & spleen
- Germinal tumors & Thymoma
- Other lymphoproliferative d/o- HCL, ALL, CLL
- Drugs & Miscellaneous
 - Phenytoin, allopurinol, atenelol, carbamazepine, gold, sul

Staging

- Clinical staging
- Pathological staging
- Laparatomy

STAGING EVALUATION OF LYMPHOMAS

- Adequate surgical biopsy
- Detailed Hx- B-symptoms
- Physical Examination
- Laboratory studies
 - CBC WITH DIFF, ESR
 - U/A
 - ORGAN FUNCTION TESTS
 - SERUM URIC ACID, Ca, LDH, Albumin
- CXR
- BM Study

- CT-SCAN, ultrasonography
- HIV
- Baseline cardiac & pulmonary function tests
- Special circumstances
 - Percutaneous or laparoscopic liver biopsy
 - Bipedal lymphangiography
 - Gallium scans & Technetium Bone scan
 - MRI & PET scan
 - Skin tests

Ann Arbor Staging System

I—involving a single lymph node region (stage I) or a single extralymphatic organ or site (stage IE)

II—two or more involved lymph node regions on the same side of the diaphragm (stage II) or localized involvement of an extralymphatic organ or site (stage IIE)

III—lymph node involvement on both sides of the diaphragm (stage III), or localized involvement of an extralymphatic organ or site (stage IIIE), or spleen (stage IIIS), or both (stage IIIES)

IV—refers to the presence of diffuse or disseminated involvement of one or more extralymphatic organs (e.g., liver, bone marrow, lung), with or without associated lymph node involvement

The presence or absence of systemic symptoms should be noted with each stage designation; A for asymptomatic; B for presence of fever, sweats, or weight loss >10% of body weight.

Cotswolds Staging Classification

<u>Classification</u>	<u>Description</u>
Stage I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localized contiguous involvement of only one extranodal organ or site and lymph node regions on the same side of the diaphragm (IIE). The number of anatomic regions involved should be indicated by a subscript (e.g., II ₃)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III _s) or by localized contiguous involvement of only one extranodal organ site (IIIE) or both (III SE)
III₁	With or without involvement of splenic, hilar, celiac, or portal nodes
III₂	With involvement of para-aortic, iliac, and mesenteric nodes
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement

Designations-any stage:

A	No symptoms
B	Fever (temperature >38°C), drenching night sweats

HODGKIN'S LYMPHOMA-HL

DEFINITION

- Formerly called Hodgkin's disease
- Hodgkin lymphoma is a group of cancers characterized by **Reed-Sternberg cells** in an appropriate **reactive cellular background**.
- HL is **B-cell neoplasm in most cases**
- Unique- malignant (RS) cells constitute **minority**
- An important clinical feature is its tendency
 - arise within lymph node areas
 - spread in an orderly fashion to **contiguous areas** of LN
- Late in the course of the disease, vascular invasion leads to widespread hematogenous dissemination.

Jackson and Parker Classification (1944)

1. Paragranuloma
2. Granuloma
3. Sarcoma

Lukes and Classification (1964)

1. Lymphocytic or histiocytic, nodular
2. Lymphocytic or histiocytic, diffuse
3. Nodular sclerosis
4. Mixed cellularity
5. Diffuse fibrosis
6. Reticular

Conference Classification (1965)

1. Lymphocyte predominance
2. Nodular sclerosis
3. Mixed cellularity
4. Lymphocytic depletion

REAL/WHO Classification (1994/2001)

1. Nodular lymphocyte predominance nodular/diffuse
2. Classic Hodgkin's lymphoma
 - Lymphocyte-rich classic HL
 - Nodular sclerosis

Epidemiology

- HL is uncommon disease
- 2-3 cases/100,000 (in US & Europe)
- Bimodal peak in the incidence
 - 1st peak 20-30yrs
 - 2nd peak 50yrs
- Histological subtype vary among different age groups
- M:F= 1.4:1

- Different pattern in developing countries
 - Earlier 1st peak
 - Mixed cellularity subtype more common
- Strong association with HIV
 - But still NON-AIDS DEFINING DISEASE
- In Ethiopia (132 adult cases studies)
 - Median age 29yrs
 - M:F 2:1

Etiology

- Cause of HL is unknown
- Association/ predisposing factors
 - EBV infection
 - HIV
 - ?Environmental & Occupation exposure
 - Genetic predisposition
 - Familial clusters
 - Identical twins

CLINICAL PRESENTATION

- Asymptomatic LAP
- Mediastinal Lap
- Splenomegaly & Hepatomegaly
- Systemic symptoms
- Other nonspecific & paraneoplastic syndromes
 - Intra-abdominal disease
 - Alcohol Induced pain
 - Cholestasis
 - Skin
 - Neurological
 - Nephrotic syndrome
 - Others – anemia, eosinophilia, thrombocytosis, leukopenia/ lymphocytosis, hypercalcemia

PATHOLOGICAL & CLINICAL FEATURES OF HL (Western Data)

HISTOLOGY SUBTYPE	(%)	AGE GROUP	PATHOLOGY	CHARACTERISTICS & STAGES AT PRESENTATION
<i>Lymphocyte-Predominant</i>	5	20-40	L&H cells, difficult pathologic Dx, Nodular form is a NON-CLASSIC HL	Males more affected, stage I-IIA, late relapses & transformation to NHL-HA
<i>Nodular sclerosis</i>	65-80	15-40	Lacunar cells, birefringent fibrotic bands	Females more affected, mediastinal, hilar & supraclavicular LAP, stage I-IIIA/B
<i>Mixed Cellularity</i>	20-35	30-50	RS cells frequent, necrosis, partial nodal involvement &	Retroperitoneal disease frequent, often symptomatic stage II-IVA/B

Sites of Disease Involvement in Untreated Patients with Hodgkin's Disease

<u>Anatomic Site</u>	<u>Involvement (%)</u>
Waldeyer's ring	1-2
Cervical nodes	60-70
Axillary nodes	30-35
Mediastinum	50-60
Hilar nodes	15-35
Para-aortic nodes	30-40
Iliac nodes	15-20
Mesenteric nodes	1-4
Inguinal nodes	8-15
Spleen	30-35
Liver	2-6
Bone marrow	1-4
Total extranodal	10-15

Treatment of HL

- Radiotherapy
- Combination chemotherapy
- Combined modality treatment
- High dose chemotherapy followed by autologous-SCT
- Allo-SCT

Definition of Treatment Groups According to the EORTC/GELA and GHSG

<u>Characteristic</u>	<u>EORTC/GELA</u>	<u>GHSG</u>
Risk factors	A: large mediastinal mass	A: large mediastinal mass
	B: age = 50 years	B: extranodal disease
	C: elevated ESR[*]	C: elevated ESR[*]
	D: =4 involved regions	D: =3 involved regions
Early stage, favorable	CS I-II, supradiaphragmatic disease with no risk factors	CS I-II with no risk factors
Early stage, unfavorable	CS I-II, supradiaphragmatic disease with one or more risk factor	CS I, CS IIA with one or more risk factors; CS IIB with C/D but without A/B
Advanced stage	CS III-IV	CS IIB with A/B; CS III-IV
Lymphocyte predominance	CS I-II, nLPHD histology, supradiaphragmatic disease	nLPHD histology in CS I-II with no risk factors

RECOMMENDATIONS FOR THE PRIMARY TREATMENT OF HODGKIN'S DISEASE OUTSIDE OF CLINICAL TRIALS

<u>Group</u>	<u>Stage</u>	<u>Recommendation</u>
Early stages (favorable)	CS I-II A/B, no RFs	4-6 cycles ABVD, EBVP <i>or</i> VBM
		± IF RT, (20-30 Gy)
Early stages (unfavorable, intermediate)	CS I-II A/B + RFs	4-6 cycles ABVD, BEACOPP-baseline, Stanford V <i>or</i> MOPP/ABV ± IF RT, 20-30 Gy
Advanced stages	CS IIB + RFs, CS III A/B, CS IV A/B	6-8 cycles ABVD, MOPP/ABV, ChIVPP/EVA, BEACOPP-escalated <i>or</i> BEACOPP-14

Drug Regimen	Dose (mg/m ²)	Route	Schedule (days)	Cycle Length
MOPP				21 days
Mechlorethamine	6	IV	1, 8	
Oncovin (vincristine)	1.4[*]	IV	1, 8	
Procarbazine	100		1-14	
Prednisone	40		1-14	
ABVD				28 days
Adriamycin (doxorubicin)	25	IV	1,15	
Bleomycin	10	IV	1,15	
Vinblastine	6	IV	1,15	
Dacarbazine	375	IV	1,15	

COPP				28 days
Cyclophosphamide	650	IV	1, 8	
Oncovin (vincristine)	1.4 [*]	IV	1, 8	
Procarbazine	100		1-14	
Prednisone	40		1-14	
Stanford V				12 weeks
Mechlorethamine	6	IV	Wk 3, 5, 9	
Adriamycin	25	IV	Wk 3, 5, 9, 11	
Vinblastine	6	IV	Wk 3, 5, 9, 11	
Vincristine	1.4 [*]	IV	Wk 2, 4, 6, 8, 10, 12	
Bleomycin	5	IV	Wk 2, 4, 6, 8, 10, 12	

BEACOPP (baseline)

Bleomycin	10
Etoposide	100
Adriamycin (doxorubicin)	25
Cyclophosphamide	650
Oncovin (vincristine)	1.4[*]
Procarbazine	100
Prednisone	40

BEACOPP (escalated)

Bleomycin	10
Etoposide	200
Adriamycin (doxorubicin)	35
Cyclophosphamide	1250
Oncovin (vincristine)	1.4[*]
Procarbazine	100
Prednisone	40
G-CSF	

Prognostic Scores for Patients with Relapsed Hodgkin's Disease

<u>Prognostic Factor</u>	<u>4-Year Overall Survival Rates</u>
Duration of first remission	
Early relapse	47%
Late relapse	73%
Stage at relapse	
Stage III/IV	46%
Stage I/II	77%
Hemoglobin level (anemia) at relapse	
F < 10.5; M < 12.0 [g/dl]	40%
F = 10.5; M = 12.0 [g/dl]	72%

Long-Term Toxicities after Curative Treatment for Hodgkin's Disease

Minor Toxicities

Endocrine dysfunctions (e.g., hypothyroidism, hypomenorrhea, amenorrhea, decreased libido)

Long-term immunosuppression

Viral infections (e.g., herpes simplex, varicella-zoster, papillomaviruses)

Serious Toxicities

Lung fibrosis from radiation therapy plus bleomycin

Myocardial damage from anthracyclines and radiation therapy

Sterility in men and women

Growth abnormalities in children and adolescents

Opportunistic infections

Psychosocial disturbances

Fatigue

Long-Term Toxicities after Curative Treatment for Hodgkin's Disease

Potentially Fatal Toxicities

Acute myeloid leukemia, myelodysplastic syndrome

Non-Hodgkin's lymphomas

Solid tumors (e.g., lung, breast, and colon cancers, sarcomas)

Overwhelming bacterial sepsis after splenectomy or splenic irradiation

NHL

Remarks

- Broad category
- Distinct lymphoid malignancies based on
 - morphology
 - Clinical behavior
 - Immunophenotype
 - Genetic markers
- Wide range from follicular to Burkitt's lymphoma

- 8 times more common
- Strongly associated with HIV
 - AIDS DEFINING ILLNESS
- Geographic clustering
 - Endemic BL
 - Adult T-cell leukemia/lymphoma
 - Small Intestinal lymphoma
 - NK-cell lymphoma

Etiology

- Etiologic consideration
 - INFECTION
 - Viral
 - Bacterial
 - Spirochetes
 - Immune Deficiency
 - Autoimmune
 - Acquired
 - congenital
 - Chemicals
 - Radiation

The indolent lymphomas

B-cell neoplasms

Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia

Lymphoplasmacytic lymphoma ($\pm$ Waldenstrom's macroglobulinemia)

Plasma cell myeloma/plasmacytoma

Hairy cell leukemia

Follicular lymphoma (grade I and II)

Marginal zone B-cell lymphoma

Mantle cell lymphoma

T-cell neoplasms

T-cell large granular lymphocyte leukemia

Mycosis fungoides

T-cell prolymphocytic leukemia

Natural killer cell neoplasms

Natural killer cell large granular lymphocyte leukemia

The aggressive lymphomas

B-cell neoplasms

Follicular lymphoma (grade III)

Diffuse large B-cell lymphoma

Mantle cell lymphoma

T-cell neoplasms

Peripheral T-cell lymphoma

Anaplastic large cell lymphoma, T/null cell

The highly aggressive lymphomas

B-cell neoplasms

Burkitt's lymphoma

Precursor B lymphoblastic leukemia/lymphoma

T-cell neoplasms

Adult T-cell lymphoma/leukemia

Precursor T lymphoblastic leukemia/lymphoma

Definition of NHL classes

- **INDOLENT**

- Survival of untreated disease measured in years
- Even CR does not lead to a cure
- Not curable with conventional treatment

- **AGGRESSIVE**

- Survival of untreated disease measured in months
- CR required for cure
- Curable with conventional treatment

- **HIGHLY AGGRESSIVE**

- Survival of untreated disease measured in weeks
- CR required for cure
- Curable with conventional treatment

Treatment

- Indolent
- Aggressive
- Highly aggressive

International Prognostic Index(IPI)

- The 5 prognostic factors in IPI
 - Age >60
 - Serum LDH level $>$ normal
 - ECOG performance status ≥ 2
 - Ann Arbor clinical stage III or IV
 - Number of involved extranodal disease sites >1
- Risk groups
 - Low risk — IPI score of zero or one
 - Low intermediate risk — IPI score of two
 - High intermediate risk — IPI score of three
 - High risk — IPI score of four or five

- Age adjusted IPI
 - Serum LDH level $>$ normal
 - ECOG performance status ≥ 2
 - Ann Arbor clinical stage III or IV
- Risk groups
 - Low risk — Age-adjusted IPI score of 0
 - Low intermediate risk — Age-adjusted IPI score of 1
 - High intermediate risk — Age-adjusted IPI score of 2
 - High risk — Age-adjusted IPI score of 3