Approach To Lymphoma

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LYMPHOMA

CLASSIFICATION

1. HODGKIN’S
   Characterised by the presence of Reed Sternberg cells

2. NON HODGKIN’S
Case 1. Primary CNS Lymphoma
Neuropathology
WHO Classification

**B-cell neoplasms**

*Precursor B-cell neoplasm*
- Precursor B-lymphoblastic leukemia/lymphoma
  (precursor B-cell acute lymphoblastic leukemia)

*Mature (peripheral) B-cell neoplasms*
- B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone B-cell lymphoma (with or w/o villous lymphocytes)
- Hairy cell leukemia
- Plasma cell myeloma/plasmacytoma
- Extranodal marginal zone B-cell lymphoma of mucosa- associated lymphoid tissue type
- Nodal marginal zone B-cell lymphoma (with or w/o monocytoid B cells)
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt's lymphoma/Burkitt's cell leukemia

**T- and NK-cell neoplasms**

*Precursor T-cell neoplasm*
- Precursor T-lymphoblastic lymphoma/leukemia
  (precursor T- cell acute lymphoblastic leukemia)

*Mature (peripheral) T-cell neoplasms*
- T-cell prolymphocytic leukemia
- T-cell granular lymphocytic leukemia
- Aggressive NK-cell leukemia
- Adult T-cell lymphoma/leukemia
  (human T-cell lymphotropic virus type I positive)
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy type T-cell lymphoma
- Hepatosplenic gammadelta T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides/Sezary syndrome
- Anaplastic large cell lymphoma, T/null-cell, primary cutaneous type
- Peripheral T-cell lymphoma, not otherwise characterized
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, T/null-cell, primary systemic type
NON HODGKIN’S LYMPHOMA
Few Questions....And still a few answers to all....

1. Am I going to die soon?
2. Why me?
3. Has it spread too much?
4. Is there any effective treatment?
5. Am I going to be fine?
Types of Lymphoma

**Indolent (low grade)**
- Life expectancy in years, untreated
- 85-90% present in Stage III or IV
- Incurable

**Intermediate**

**Aggressive (high grade)**
- Life expectancy in weeks, untreated
- Potentially curable
Etiology of NHL

- Immune suppression
  - congenital (Wiskott-Aldrich)
  - organ transplant (cyclosporine)
  - AIDS
  - increasing age

- DNA repair defects
  - ataxia telangiectasia
  - xeroderma pigmentosum
Etiology of NHL

• Chronic inflammation and antigenic stimulation
  – Helicobacter pylori inflammation, stomach
  – Chlamydia psittaci inflammation, ocular adnexal tissues
  – Sjögren’s syndrome

• Viral causes
  – EBV and Burkitt’s lymphoma
  – HTLV-I and T cell leukemia-lymphoma
  – HTLV-V and cutaneous T cell lymphoma
  – Hepatitis C
Epidemiology

• Indolent lymphomas - rare in young people
• Large cell lymphoma (DHL) – commonest lymphoma
• Burkitt’s and lymphoblastic lymphoma are common in adolescents.
• AIDS patients develop aggressive, high grade lymphomas.
Clinical Features

- Lymphadenopathy
- Cytopenias
- Systemic symptoms
- Hepatosplenomegaly
- Fever
- Night sweats
Diagnosis of NHL

• **Excisional biopsy** is a must

• **Immunohistochemistry** to confirm cells are lymphoid
  – LCA (leukocyte common antigen)
  – Monoclonal staining with Igκ or Igλ

• **Flow cytometry**:
  – CD 19, CD20 for B cell lymphomas
  – CD 3, CD 4, CD8 for T cell lymphomas
Diagnosis of NHL

• **Chromosome changes**
  – 14;18 translocation in follicular lymphoma
  
  – t(8;14), t(2;8), t(8;22) in Burkitt’s lymphoma

  – t(11;14) in mantle cell lymphoma
Staging Workup

- Complete Blood Count (CBC)
- Biochemical investigations (UA, LDH, LFT, Creat, K+)
- CT scans of chest, abdomen and pelvis
- PET CT scan
- Bone marrow biopsy and aspirate
- (Lumbar puncture)
  - AIDS lymphoma
  - T cell lymphoblastic lymphoma
  - High grade lymphoma with positive marrow
Staging: Ann Arbor

I.  1 lymph node region or structure
II. >1 lymph node region or structure, same side of diaphragm
III. Both sides of diaphragm
IV. Extranodal sites beyond “E” designation

subscripts: A, B, E, S
INTERNATIONAL PROGNOSTIC INDEX (IPI)

- **Age** - <= 60 vs. > 60
- **Performance status** ----<2 vs. > 2
- **LDH** ---→ < 1 x Normal vs. > 1 x Normal
- **Extranodal Disease** ---< /=1 vs. > 1
- **Stage of Disease** ----I / II vs. III /IV

APLES

Age adjusted IPI (aIPI) – No AE
International Prognostic Index

LOW
LOW – INTERMEDIATE
HIGH – INTERMEDIATE
HIGH

0 or 1
2
3
4 or 5
### TABLE 6 International Prognostic Index

<table>
<thead>
<tr>
<th>Number of Risk Factors</th>
<th>Complete Response Rate (%)</th>
<th>Five-year Relapse-free Survival (%)</th>
<th>Five-year Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0 or 1</td>
<td>87</td>
<td>70</td>
</tr>
<tr>
<td>Low intermediate</td>
<td>2</td>
<td>67</td>
<td>50</td>
</tr>
<tr>
<td>High intermediate</td>
<td>3</td>
<td>55</td>
<td>49</td>
</tr>
<tr>
<td>High</td>
<td>4 or 5</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>Age-adjusted index, patients ≤60 years†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
<td>Low intermediate</td>
<td>1</td>
<td>78</td>
<td>66</td>
</tr>
<tr>
<td>High intermediate</td>
<td>2</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>46</td>
<td>58</td>
</tr>
</tbody>
</table>

*Adverse factors: age > 60 years, increasing lactate dehydrogenase, performance status 2 to 4, more than one extranodal site, Ann Arbor Stage III or IV.

†Adverse factors: elevated lactate dehydrogenase, performance status 2 to 4, Ann Arbor Stage III or IV.
TUMOR LYSIS SYNDROME

- Hypekalaemia
- Hyperuricaemia
- Hyperphosphphataemia
- Hypocalcaemia
- Renal failure

- Sodium bicarbonate – 600 mg 3 times a day (10 mg/kg/day 3 times a day)
- Allopurinol – 300 mg once a day (5-6 mg/kg/day)
- Adequate hydration
- Rasburicase
## NON HODGKINS LYMPHOMA
### CHOP

<table>
<thead>
<tr>
<th></th>
<th><strong>Level A</strong></th>
<th><strong>Level B</strong></th>
<th><strong>Level C</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adriamycin</td>
<td>50 mg/m2</td>
<td>35 mg/m2</td>
<td>25 mg/m2 iv Day 1</td>
</tr>
<tr>
<td>2. Vincristine</td>
<td>1.4 mg/m2</td>
<td>1.4 mg/m2</td>
<td>1.4 mg/m2 iv Day 1</td>
</tr>
<tr>
<td>3. Cyclophosphamide</td>
<td>800 mg/m2</td>
<td>400 mg/m2</td>
<td>200 mg/m2 iv Day 1</td>
</tr>
<tr>
<td>4. Prednisolone</td>
<td>60 mg/m2</td>
<td>60 mg/m2</td>
<td>60 mg/m2 p/o Days 1-5</td>
</tr>
</tbody>
</table>

Repeat at 21 Day intervals for 6 cycles and restage.
Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma

CHOP IS STANDARD OF CARE
RITUXIMAB
Long-Term Results of the R-CHOP Study in the Treatment of Elderly Patients With Diffuse Large B-Cell Lymphoma: A Study by the Groupe d’Etude des Lymphomes de l’Adulte

R-CHOP IS STANDARD OF CARE
## NON HODGKINS LYMPHOMA
### R - CHOP

**RITUXIMAB – 375 mg /m² on DAY 1**

<table>
<thead>
<tr>
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<th>Level B</th>
<th>Level C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adriamycin</td>
<td>50 mg/m²</td>
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</tr>
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</tr>
<tr>
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<td>800 mg/m²</td>
<td>400 mg/m²</td>
<td>200 mg/m²</td>
</tr>
<tr>
<td>4. Prednisolone</td>
<td>60 mg/m²</td>
<td>60 mg/m²</td>
<td>60 mg/m²</td>
</tr>
</tbody>
</table>

6 cycles at an interval of 21 days

**CHOP PER CYCLE – Rs. 5000 / -
R-CHOP PER CYCLE – Rs. 45,000 / -**
Figure 4. Overall survival of patients with follicular lymphoma treated at St Bartholomew’s Hospital (SBH), London.
Follicular Lymphoma International Prognostic Index

1. AGE - <60 vs. > 60 years
2. Stage – I / II vs. III / IV disease
3. Hb% - > 12 gm% vs. < 12 gm%
4. Nodal site - < /= 4 vs. > 4 areas
5. LDH – Above normal vs. Normal

LOW – 0 -1
INTERMEDIATE – 2
HIGH – >=3

Blood. 2004;104:1258-1265
Reasons to Treat in Advanced Indolent Lymphomas

- Constitutional symptoms
- Anatomic obstruction
- Organ dysfunction
- Cosmetic considerations
- Painful lymph nodes
- Cytopenias

STAGE I / II – ABOUT 40% CURABLE WITH RADIOTHERAPY
Treatment Options: *Indolent lymphomas*

- 10-15% in Stage I or II
  - Potentially curable
  - Local radiotherapy
- 85-90% Stage III or IV
  - Incurable
  - Treatment does not prolong survival
Treatment Options in Advanced Indolent Lymphomas

- Observation only.
- Radiotherapy to site of problem.
- Systemic chemotherapy
  - oral agents: chlorambucil and prednisone
  - IV agents: CHOP, COP, fludarabine, 2-CDA.
- Antibody against CD20: Rituxan, Bexxar, Zevalin.
- Stem cell or bone marrow transplant.
Follow Up - 3 scenario

- **IN Remission** – Follow up 1\textsuperscript{st} 3 monthly and then 6 monthly for 5 years

- Progressive disease / Refractory disease – Palliation vs. Definitive treatment

- Relapse after achieving CR / PR – Palliation vs. Definitive therapy
DEFINITIVE THERAPY

- Salvage Chemotherapy followed by Autologous stem cell transplantation
- Salvage chemotherapy
  - RICE
  - DHAP
  - ICE
  - MINE
  - MIME
- 2-3 cycles of salvage chemotherapy
- 50% cure rate with chemo sensitive diseases
Thomas Hodgkin, in 1832, ... when he described this disease for the first time, had a rather dull armentarium to treat this sickness: surgery, herbs, arsenic acid and mainly tender loving care.

Dorothee Reed, 70 yr later wrote:

...the treatment for this disease is dismal. All patients die within 3–4 yr. Even if you resect the tumor totally, it will recur and grow even faster than before...and finally the patient dies of cachexia or due to tuberculosis or other fatal infections...
• MOPP Chemotherapy -1960 – NCI – **Hypothesis** was cancer can be cured
• 1970 – Answer was **YES** – No more Hypothesis

*Fig. 1.* Progress made in the treatment of advanced stage Hodgkin’s lymphoma during the last century; data modified from de Vita including data from GHSG HD9 trial.
INTERNATIONAL PROGNOSTIC FACTORS

- Age $\geq 45$ years
- Sex – Male
- Stage – IV
- Haemoglobin - $< 10.5$ gm%
- TWBC count - $> 15 \times 10^9 / L$
- Lymphocyte count - $< 0.6 \times 10^9 / L$ or $< 8\%$ of white cell differential
- Serum Albumin $< 4$ g/dl

HASENCLEVER INDEX
Table 1
Definition of treatment groups according to the European Organization for Research and Treatment of Cancer/Groupe d’Etude des Lymphomes de l’Adulte, German Hodgkin’s Lymphoma Study Group, and National Cancer Institute of Canada/Eastern Cooperative Oncology Group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>EORTC/GELA</th>
<th>GHSG</th>
<th>NCIC/ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stage favorable</td>
<td>CS I–II without risk factors (supradiaphragmatic)</td>
<td>CS I–II without risk factors</td>
<td>Standard risk group: favorable</td>
</tr>
<tr>
<td>Early stage unfavorable</td>
<td>CS I–II with ≥1 risk factor (supradiaphragmatic)</td>
<td>CS I, CSIIA ≥1 risk factors; CS IIB with C/D but without A/B</td>
<td>Standard risk group: unfavorable</td>
</tr>
<tr>
<td>Advanced stage</td>
<td>CS III–IV</td>
<td>CS IIB with A/B; CS III–IV</td>
<td>High risk group:</td>
</tr>
<tr>
<td>Risk factors (RF)</td>
<td>A. Large mediastinal mass</td>
<td>A. Large mediastinal mass</td>
<td>A. ≥40 years</td>
</tr>
<tr>
<td></td>
<td>B. Age ≥50 years</td>
<td>B. Extranodal disease</td>
<td>B. Not NLPHL or NS histology</td>
</tr>
<tr>
<td></td>
<td>C. Elevated ESR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C. Elevated ESR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C. ESR ≥50 mm/h</td>
</tr>
<tr>
<td></td>
<td>D. ≥4 involved regions</td>
<td>D. ≥3 involved areas</td>
<td>D. ≥4 involved nodal regions</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; GELA, Groupe d’Etude des Lymphomes de l’Adulte; GHSG, German Hodgkin Study Group; NCIC, National Cancer Institute of Canada; NLPHL, nodular lymphocyte predominance; NS, nodular sclerosis.

<sup>a</sup>Erythrocyte sedimentation rate (≥50 mm/h without or ≥30 mm/h with B symptoms).
**Table 6. Brief ABVD Chemotherapy Followed by Radiation for Limited-Stage Hodgkin’s Lymphoma**

<table>
<thead>
<tr>
<th></th>
<th>Milan\textsuperscript{10}</th>
<th>Vancouver\textsuperscript{11}</th>
<th>GHSG\textsuperscript{*12}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible stages</td>
<td>IA, IB, IIA</td>
<td>IA, IIA</td>
<td>IA, IIA</td>
</tr>
<tr>
<td>No. of patients</td>
<td>140</td>
<td>268</td>
<td>204</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>87</td>
<td>67</td>
<td>22</td>
</tr>
<tr>
<td>ABVD treatment, months</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Radiotherapy field</td>
<td>Involved or extended</td>
<td>Extended, 1989-1997; involved, 1997-2004</td>
<td>Extended</td>
</tr>
<tr>
<td>Disease-free survival, %</td>
<td>95</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>Overall survival, %</td>
<td>93</td>
<td>97</td>
<td>98</td>
</tr>
</tbody>
</table>

Abbreviations: GHSG, German Hodgkin Study Group; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.

*Only patients with absence of unfavorable prognostic factors were included in the GHSG study.*
Early Interim $2\cdot[^{18}\text{F}]\text{Fluoro-2-Deoxy-D-Glucose}$ Positron Emission Tomography Is Prognostically Superior to International Prognostic Score in Advanced-Stage Hodgkin’s Lymphoma: A Report From a Joint Italian-Danish Study

**Fig 2.** Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group.
Fig 3. (A) Overall survival of patients with peripheral T-cell lymphoma (PTCL) not otherwise specified (NOS) by the standard International Prognostic Index. (B) Overall survival of the patients with PTCL-NOS who were treated with or without an anthracycline-based induction therapy. (C) Overall survival of the patients with angioimmunoblastic type who were treated with or without an anthracycline-based induction therapy.

PTCL, natural killer/T-cell lymphoma, ATLL, adult T-cell leukemia/lymphoma, ALCL, anaplastic large-cell lymphoma, NM, not applicable.
Table 1. Clinical subdivision of noncutaneous, mature T/NK neoplasms, unique features, and expected 5-year survival.

<table>
<thead>
<tr>
<th></th>
<th>Unique Features</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nodal</strong></td>
<td><strong>Anaplastic large cell, ALK-positive</strong></td>
<td>60-90</td>
</tr>
<tr>
<td></td>
<td>t(2;5)(p23;q35) and variants; extranodal involvement (50-80%), skin (21-35%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Anaplastic large cell, ALK-negative</strong></td>
<td>10-45</td>
</tr>
<tr>
<td></td>
<td>Distinguish from primary cutaneous anaplastic large cell lymphoma (ALCL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Angioimmunoblastic</strong></td>
<td>10-30</td>
</tr>
<tr>
<td></td>
<td>Autoimmunity</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Peripheral T-cell lymphoma, unspecified</strong></td>
<td>15-35</td>
</tr>
<tr>
<td></td>
<td>Most common, survival dependent on IPI</td>
<td></td>
</tr>
<tr>
<td><strong>Extranodal</strong></td>
<td><strong>Nasal</strong></td>
<td>50-70</td>
</tr>
<tr>
<td></td>
<td>Localized</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disseminated (nasal type)</td>
<td>5-10</td>
</tr>
<tr>
<td></td>
<td>Sites: skin, gastrointestinal tract, testis, orbit</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Enteropathy associated</strong></td>
<td>5-20</td>
</tr>
<tr>
<td></td>
<td>Celiac disease; small bowel obstruction</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Hepatosplenic, γδ</strong></td>
<td>5-15</td>
</tr>
<tr>
<td></td>
<td>Isochromosome 7, trisomy 8; can occur in organ transplants</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Subcutaneous panniculitis-like</strong></td>
<td>10-30</td>
</tr>
<tr>
<td></td>
<td>Aggressive with hemophagocytosis; may be indolent</td>
<td></td>
</tr>
<tr>
<td><strong>Leukemia</strong></td>
<td><strong>T-Prolymphocytic leukemia</strong></td>
<td>10-20</td>
</tr>
<tr>
<td></td>
<td>Chromosome 14 abnormalities</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Adult T-cell lymphoma/leukemia</strong></td>
<td>0-15*</td>
</tr>
<tr>
<td></td>
<td>HTLV-1 association, hypercalcemia. Four types: acute (55-65%), chronic,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>smoldering leukemia and lymphoma (20-25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Large granular lymphocytic leukemia</strong></td>
<td>50-75</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis, neutropenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Aggressive NK leukemia</strong></td>
<td>0-10</td>
</tr>
<tr>
<td></td>
<td>May represent leukemic phase of extranodal NK neoplasms (nasal type)</td>
<td></td>
</tr>
</tbody>
</table>

*Survival pertains to the acute leukemia and lymphoma presentations of ATLL
THANK YOU