LYMPHOMA: DEFINITION, DIAGNOSIS AND TREATMENT

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Chair,
LWP of the EBMT
• General introduction
• Hodgkin lymphoma
• Non Hodgkin lymphoma
  – Follicular lymphoma (‘indolent’)
  – Diffuse large B-cell lymphoma (‘aggressive’)

European Group for Blood and Marrow Transplantation
Lymphoma. Definition

HETEROGENEOUS group of malignant neoplasms arising in the reticuloendothelial and lymphoid system.

- Hodgkin lymphoma
- Non-Hodgkin lymphomas

Hodgkin lymphoma and Non-Hodgkin lymphomas overlap.
Clinical features

- Lymph node enlargement
- Hepato-splenomegaly
- BM involvement - cytopenias
- B-symptoms
- Infiltration of other organs
- Compression symptoms


**Diagnosis and staging**

**Diagnosis:**
- Tissue **BIOPSY** *(not an FNA)*

**Staging:**
- FBC
- Biochemistry *(including LDH)*
- Virology *(including HIV 1 and 2)*
- NCAP CTscan/ FDG PETscan
- BM biopsy
Why a biopsy?

Follicular Lymphoma

Diffuse large B-cell lymphoma

Follicular Lymphoma

Diffuse large B-cell lymphoma
Ann Arbor stage

- **Stage I**: involvement of a single lymphoid or extralymphoid (IE) site.
- **Stage II**: involvement of more than one lymphoid sites on the same side of the diaphragm.
- **Stage III**: involvement of lymphoid sites on both sides of diaphragm.
- **Stage IV**: disseminated disease with involvement of one or more extranodal sites.

E: contiguous extranodal disease; A/B: absence or presence of B-symptoms (weight loss/fever/night sweats); X: bulky disease (>10cm/ >1/3 thoracic diameter)
Prognostics factors

- Age
- Histology & Biology
- Tumor burden
- Associated diseases
- PS
**Prognostic Scores for Lymphomas**

<table>
<thead>
<tr>
<th>Advanced Stage HL (‘Hasenclever Index’)</th>
<th>DLBCL (IPI)</th>
<th>FL (FLIPI)</th>
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</thead>
<tbody>
<tr>
<td>- Serum albumin</td>
<td>- Age</td>
<td>- Age</td>
</tr>
<tr>
<td>- Hb</td>
<td>- Serum LDH</td>
<td>- Serum LDH</td>
</tr>
<tr>
<td>- Sex (male)</td>
<td>- Performance status</td>
<td>- Hb</td>
</tr>
<tr>
<td>- Stage</td>
<td>- Stage</td>
<td>- Stage</td>
</tr>
<tr>
<td>- Age</td>
<td>- Extra-nodal sites</td>
<td>- Nodal sites</td>
</tr>
<tr>
<td>- WBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Lymphocyte count</td>
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</tbody>
</table>
HODGKIN LYMPHOMA
Epidemiology

- ≈1500 new cases every year in the UK
  ⇒ Incidence: 3/100,000/year
- Bi-modal age distribution: 15-34 yrs, > 60 yrs
- Male/female ratio: 1.4:1
Hodgkin lymphoma. Classification

- Lymphocyte rich
- Nodular sclerosis
- Mixed cellularity
- Lymphocyte depleted
Clinical features

- Lymph node enlargement
- Mediastinal mass
- B-symptoms
- Pruritus
- Alcohol-induced adenopathic pain
Mediastinal mass

BUT NO SVC0!!
Stage matters

Early stage

Advanced stage

χ² = 15.41

P = .0015

I N= 89
II N= 164
III N= 134
IV N= 71
## But ...

<table>
<thead>
<tr>
<th></th>
<th>EORTC/GELA</th>
<th>GHSG</th>
<th>NCIC/ECOG</th>
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</thead>
<tbody>
<tr>
<td>Early stage favourable</td>
<td>CS I-II</td>
<td>CS I-II</td>
<td>CS I-II</td>
</tr>
<tr>
<td></td>
<td>no RF</td>
<td>no RF</td>
<td>no RF</td>
</tr>
<tr>
<td>Early stage unfavourable</td>
<td>CS I-II</td>
<td>CS I-IIA</td>
<td>CS I-II</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 RF</td>
<td>&gt; 1 RF; CS IIIB with C/D (no A/B)</td>
<td>&gt; 1 RF</td>
</tr>
<tr>
<td>Advanced stage</td>
<td>CS III-IV</td>
<td>CS IIB with A/B; CS III-IV</td>
<td>CS I-II bulky/abd; CS III-IV</td>
</tr>
</tbody>
</table>

**Risk factors (RF):** EORTC/ GELA (bulky med, >50 yrs, high ESR, >4 areas); GHSG (A: bulky med B: extranodal C: high ESR D: >3 areas); NCIC/ECOG: (>40 yrs, no NLPHL, high ESR, >4 areas)
Outcome of HL patients

Barts, 1970-1985
But....

N: 2,498

Death from HL

Other causes

Stanford University, 1960-1995
1st Line Treatment in Patients with Hodgkin’s Lymphoma

Chemotherapy
±
Radiotherapy
Irradiation Fields in Hodgkin’s Lymphoma

- Involved field
- Extended field
- Total nodal irradiation
Therapeutic Objectives in Patients with Localized Stages

- Improve survival curves
- Minimize long-term side effects
What About Patients in Advanced Stages?

The “gold standard” ABVD

- Adriamicine 25 mg/m^2 iv (days 1 & 15)
- Bleomicine 10 mg/m^2 iv (days 1 & 15)
- Vinblastine 6 mg/m^2 iv (days 1 & 15)
- Dacarbazine 375 mg/m^2 iv (days 1 & 15)

Has been challenged by other more intensive protocols

- Escalated and baseline BEACOPP
- Stanford V
Prognosis of HL has Significantly Improved over Years

- Cured (60%)
- Relapse (30%)
- Primary Refractory (10%)

Other Therapeutic Alternatives
Therapeutic options for Relapsed Patients

- Radiotherapy
- Salvage Chemotherapy and ASCT
- Allogeneic Stem Cell Transplantation
- New drugs
Freedom from Treatment Failure for chemo-sensitive patients after early relapse

at 7 years:
A: n.a.
B: 42% [21%, 64%]

Schmitz et al, ASCO, 2005
RIC-Allo for HL: Identification of Factors Predicting Outcome

PFS and OS for patients with chemosensitive disease and good performance status at SCT treated with a RIC SCT in the period 2002-2005 (n=104).

Robinson et al. Haematol 2009

Months after RIC

PFS

Months after RIC-SCT

Overall Survival

45% at 3 Y

60%
NON-HODGKIN LYMPHOMAS
Epidemiology

- ≈ 9000 new cases every year in the UK
  ⇒ Incidence: 20/ 100,000/ year
- Median age at diagnosis: 65 yrs
- Male/ female ratio: 1.5:1
**WHO classification**

**Mature B-Cell Neoplasms**
- Chronic lymphocytic leukemia / small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Lymphoplasmacytic lymphoma / Waldenstrom macroglobulinemia
- Heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma
- Extramedullary marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type
- Nodal marginal zone lymphoma
- Follicular lymphoma
- Primary cutaneous follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma, NOS (T-cell / Histiocyte-rich)
- Diffuse large B-cell lymphoma with chronic inflammatory background
- Lymphomatoid granulomatosis
- Primary mediastinal large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK+ large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma associated with HIV / AIDS
- Primary effusion lymphoma
- Burkitt lymphoma
- B cell lymphoma, urticarial, Burkitt-like
- B cell lymphoma, unclassifiable, diffuse in lymphoma-like

**Mature T-Cell & NK-Cell Neoplasms**
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK-cells.
- Aggressive NK-cell leukemia
- Systemic EBV+ T-cell lymphoproliferative disorder of childhood
- Adult T-cell lymphoma/leukemia
- Extramedullary T/NK-cell lymphoma, nasal type
- Castleman disease
- Hepato-splenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30+ T-cell lymphoproliferative disorder
- Primary cutaneous gamma-delta T-cell lymphoma
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK+ type
- Anaplastic large cell lymphoma, ALK- type
- **Hodgkin lymphoma (Hodgkin disease)**
  - Nodular lymphocyte-predominant Hodgkin lymphomas
  - Classic Hodgkin lymphomas
  - Nodular sclerosis Hodgkin lymphoma
  - Lymphocyte-rich classic Hodgkin lymphoma
  - Mixed cellularity Hodgkin lymphoma
  - Lymphocyte depletion Hodgkin lymphoma
- **Post-Transplant Lymphoproliferative Disorders (PTLD)**
  - Plasmacytic hyperplasia
  - Infectious mononucleosis like PTLD
  - EBV-like PTLD
  - Hematopoietic PTLD (e.g., T/NK cell types)
  - Classic HD type PTLD
- **Histiocytic and Dendritic Cell Neoplasms**
- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Indeterminate dendritic cell sarcoma
- Disseminated juvenile xanthogranuloma

**AIM to define specific entities according to:**
- **Morphology**
- **Immunophenotypic**
- **Molecular biology**
- **Genetic**
- **Clinical presentation and course**

**European Group for Blood and Marrow Transplantation**
REAL/ WHO Classification

N=1403

NHL Classification Project, 1997
NHL’s overall survival

5-yr OS >70%

5-yr OS <30%

NHL Classification Project, 1997
The GOLD STANDARD: CHOP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m²</td>
<td>i.v.</td>
<td>day 1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50 mg/m²</td>
<td>i.v.</td>
<td>day 1</td>
</tr>
<tr>
<td>Vincristin</td>
<td>1.4 mg/m² (max. 2)</td>
<td>i.v.</td>
<td>day 1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>100 mg</td>
<td>p.o.</td>
<td>day 1-5</td>
</tr>
</tbody>
</table>

repeat: day 22

McKelvey et al, 1976
The GOLD STANDARD: rituximab

Pan-B-cell antibody against the CD20 antigen

= Rituximab
FOLLICULAR LYMPHOMA
Follicular lymphoma.
Clinical characteristics

- Median age: 50-60 yrs
- Good performance status
- Advanced stage: 80%
- BM infiltration: 60%
- Often, longstanding waxing and waning lymphadenopathies
Natural history and clinical course

Johnson et al, JCO, 1995

Barts, 1972-1999
Overall survival (OS) and time to treatment failure (TTF)

Hospital Clínic, Barcelona
First-line therapy of follicular lymphoma

- **watch & wait („live with the disease“)**
- **non-curative immuno-chemotherapy** in symptomatic cases:
  - B-symptoms
  - hematopoietic insufficiency
  - hyperviscosity syndrome
  - local LN compression
  - rapid progress
- **cure may be possible by aggressive immuno-chemotherapy**
CHOP ± rituximab in previously untreated follicular lymphoma (FL): study design

6–8 x CHOP + rituximab

CR, PR

6–8 x CHOP

CR, PR

Patients <60 years

PBSCT

Standard IFN-maintenance

Patients >60 years

Intensive IFN-maintenance

Standard IFN-maintenance


CR = complete response; PR = partial response
R-CHOP versus CHOP in previously untreated follicular NHL: TTF

TTF = time-to-treatment failure

R-CHOP versus CHOP in previously untreated follicular NHL: overall survival (OS)

CUP Trial

Long-term outcomes after reduced-intensity conditioning allogeneic stem cell transplantation for low-grade lymphoma: a survey by the French Society of Bone Marrow Graft Transplantation and Cellular Therapy (SFGM-TC)

Stéphane Vigouroux, Mauricette Michallet, Raphaël Porcher, Michel Attal, Lionel Ades, Marc Bernard, Didier Blaise, Reza Tabrizi, Frédéric Garban, Jill-Patrice Cassuto, Patrice Chevalier, Thierry Facon, Norbert Ifrah, Marc Renaud, Hervé Tilly, Jean-Paul Vernant, Mathieu Kuentz, Jean-Henri Bourhis, Pierre Bordigoni, Eric Deconinck, Bruno Lioure, Gérard Socié, Noël Milpied
DIFFUSE LARGE B-CELL LYMPHOMA
**Diffuse large B cell lymphoma.**

**Clinical characteristics**

- Median age: 60-70 years
- Advanced stage: 50-60%
- BM involvement: 15-20%
- Primary extranodal: 20-30%
- Rapidly growing masses
Overall survival (OS) and disease-free survival (DFS)
DLBCL, outcome

ADVANCED DIFFUSE HISTIOCYTIC LYMPHOMA, A POTENTIALLY CURABLE DISEASE

RESULTS WITH COMBINATION CHEMOTHERAPY

Vincent T. DeVita, Jr.  George P. Canellos
Bruce Chabner         Philip Schein *
Susan P. Hubbard      Robert C. Young

Medicine Branch, National Cancer Institute,
National Institutes of Health, Bethesda,
Maryland 20014, U.S.A.

Lancet, February 1, 1975
Survival of patients < 60 years and IPI 0/1 after (R-)CHO(E)P

- **R-CHEMO** (n=413)
  - Median follow-up: 34 months
  - 93% survival

- **CHEMO** (n=410)
  - 84% survival

**p = 0.0001**
DSHNHL 2002-1 -- R-MegaCHOEP
study design after amendment 1 for CD20-pos. B-NHL

Rituximab (375mg/m²)

PRD and VCR doses are absolute, all others are per m²
DSHNHL 2002-1 -- MegaCHOEP
Event-free survival

p = 0.050
**CORAL Trial: RICE vs. DHAP**

- **CD20+ DLBCL**
  - Relapsed/Refractory

**Randomize**

- **R-ICE x 3**
- **SD/PD → Off**
- **PR/CR → R x 6**
- **Obs**

- **R-DHAP x 3**
PROGRESSION-FREE SURVIVAL ACCORDING TO FAILURE FROM DIAGNOSIS (INDUCTION ITT)

- Failure from diagnosis <12 months: 64% (N=160)
- Failure from diagnosis ≥12 months: 31% (N=228)

PROGRESSION-FREE SURVIVAL ACCORDING TO PRIOR RITUXIMAB (INDUCTION ITT)

- Prior rituximab: No: 62% (N=147)
- Prior rituximab: Yes: 30% (N=241)

p<0.0001
The role of intensive therapies in lymphomas

More effective first line therapies (CT + R) / Maintenance therapies

Newer drugs (R / Z)

Lack of prospective clinical trials in the “new era”

Information regarding “old prospective clinical trials” not applicable nowadays