Introduction to the Biology and Management of Lymphoproliferative Disorders

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What is lymphoma?

Trends over time.....we are making a difference!
Lymphocyte development is a complex process that occurs in discrete steps.\textsuperscript{1-3}

Myeloid progenitor

B cell

Plasma cell

Mature dendritic cell

Myeloid progenitor

DC stem cell

Mature dendritic cell

Myeloid series

Monocytes

Macrophages

Neutrophils


ALL

CLL

Lymphomas

MM

B-lymphocytes

T-lymphocytes

A-lymphocytes

Myeloproliferative disorders

AML

Neutrophils

Eosinophils

Basophils

Monocytes

Plasma cells

Red cells

Stages of B-cell development

...
**Cellular origin of B-cell lymphomas**

- Marginal zone lymphoma
- B-cell lymphoma
- Mantle cell lymphoma
- Follicular lymphoma
- Burkitt lymphoma
- DLBCL (some)
- Hodgkin lymphoma
- Mantle cell lymphoma
- Pro/pre plasma cell
- Mature plasma cell

**Lymphoma subtypes arise from different stages of B-cell development**

- Bone marrow
- Interfollicular area
- Follicular area
- Perifollicular area

**Stages of B-cell development are defined by surface antigen expression**

- B cell
- Pro B cell
- Plasma cell
- CD19
- CD20
- CD21
- CD22
- CD38
- CD40
Table 2 NK and T-cell subsets and the classification of peripheral T-cell and NK-cell neoplasms

<table>
<thead>
<tr>
<th>Innate immune system</th>
<th>Adaptive immune system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not require antigen sensitization</td>
<td>Characterized by specificity and memory</td>
</tr>
<tr>
<td>NK cells, NK/T cells, γδ T cells</td>
<td>Effector and memory T cells</td>
</tr>
<tr>
<td>Cell-mediated cytotoxicity</td>
<td>Act principally through cytokines and chemokines</td>
</tr>
<tr>
<td>Mainly cutaneous and other extranodal sites</td>
<td>Mainly nodal lymphomas</td>
</tr>
<tr>
<td>Children and adults</td>
<td>More often in adults</td>
</tr>
</tbody>
</table>

- Aggressive NK cell leukemia
- Systemic EBV positive T-cell lymphoproliferative disease
- Hepatosplenic γδ TCL
- Most other T cell lymphomas
Stages of T-cell development are defined by surface antigen expression

<table>
<thead>
<tr>
<th>Prothymocyte</th>
<th>Cortical Thymocyte</th>
<th>Medullary Thymocyte</th>
<th>T-cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD7</td>
<td>CD2/CD5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDT*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Terminal deoxynucleotidyl transferase


Transforming events

- Reciprocal chromosomal translocations
  - Oncogene comes under control of active Ig Locus, causing a deregulated, constitutive expression of oncogene
- Mutations in tumor suppressor genes
- Genomic amplifications (such as REL)
- Translocations not involving Ig loci
- Viruses

Genetic alterations determine lymphoma entities
Classification

- Historically - a mess
  - 1940s Gail and Mallory
  - 1950s Rappaport
  - 1970s Lukes-Collins
  - 1970s Kiel
  - 1982 Working
  - 1994 REAL
  - WHO - currently used

WHO classification for lymphomas

- Universal, consensual
- Collaborative work between clinicians & pathologists from different countries
- Accurate criteria, updated
- All haematopoietic neoplasms (NHL, Hodgkin, myeloid & histiocytic neoplasms)

- About ~60 entities of lymphomas

Lymphoma classification (WHO)

- B-cell neoplasms
  - precursor
  - mature
- T-cell & NK-cell neoplasms
  - precursor
  - mature
- Hodgkin lymphoma

Non-Hodgkin Lymphomas
Lymphoma is a heterogeneous disease comprised of multiple subtypes

Non-Hodgkin lymphoma (NHL) 70,130
Hodgkin lymphoma (HL) 9,060

Risk factors for NHL
- immunosuppression or immunodeficiency
- connective tissue disease
- infectious agents
- ionizing radiation
Clinical manifestations

- Variable
  - severity: asymptomatic to extremely ill
  - time course: evolution over weeks, months, or years
- Systemic manifestations
  - fever, night sweats, weight loss, anorexia, pruritis
- Local manifestations
  - lymphadenopathy, splenomegaly most common
  - any tissue potentially can be infiltrated

Other complications of lymphoma

- bone marrow failure (infiltration)
- CNS infiltration
- immune hemolysis or thrombocytopenia
- compression of structures (eg spinal cord, ureters)
- pleural/pericardial effusions, ascites

How to make the diagnosis?
History and physical: suspect lymphoid malignancy

Laboratory tests
Diagnostic imaging
Lymph node biopsy

Fresh biopsy tissue:
- Flow cytometric immunophenotyping
- Cytogenetics/molecular genetics
- Snap-freeze for future studies

Paraffin-embedded tissue:
- Routine formalin fixation
- Immunohistochemistry
- FISH (whole sections or disaggregated nuclei)

Case study 1

- A 50 year old previously healthy man presents with rapidly enlarging right sided neck lymph node for the past 1 month. He has lost 10 lb despite a good appetite and reports drenching night sweats.
- On exam, he has a 5 cm left cervical LN.
- No LAP elsewhere.
- No hepatosplenomegaly

Labs show a LDH of 1600, rest wnl.
PET-CT
Lymph node biopsy

Histopathology

Immunohistochemistry

Immunophenotyping lymphomas involves multiple cell surface antigens\(^1,2\)

B cells
Kappa
CD20
CD10

Lambda
CD45

T cells
CD2
CD3
CD4
CD7
CD8
CD56
CD10
CD19
CD20

Molecular diagnostics- MYC and BCL2 rearrangements

Final diagnosis
Till 2015: Double hit DLBCL
2016 onwards: High grade B-cell lymphoma with myc and BCL2 rearrangements

Treatment: high dose chemotherapy +/- autologous stem cell transplant
Case study 2

- A 75 year old man presents with a cervical LN which has been growing gradually for past 2 years. Over the past year, he has also noticed swellings in his groin on both sides.
- On exam he has non-tender cervical and inguinal lymphadenopathy.
- Labs (including LDH) are normal

PET scan

LN biopsy

Histopathology

Immunohistochemistry
Final diagnosis: Follicular lymphoma grade 1-2

- Treatment: Watchful expectancy

Lymphoma Biology

- **Aggressive NHL**
  - short natural history (patients die within months if untreated)
  - disease of rapid cellular proliferation, cured with intensive combination chemotherapy regimens

- **Indolent NHL**
  - relatively good prognosis, long natural history (patients can live for many years untreated)
  - disease of slow cellular accumulation, not curable

Ann Arbor Staging of lymphoma

- **Stage I**
- **Stage II**
- **Stage III**
- **Stage IV**

A: absence of B symptoms
B: fever, night sweats, weight loss
Three common lymphomas

- Follicular lymphoma
- Diffuse large B-cell lymphoma
- Hodgkin lymphoma

Follicular lymphoma

- most common type of “indolent” lymphoma
- usually widespread at presentation
- often asymptomatic
- not curable (some exceptions)
- associated with BCL-2 gene rearrangement \([t(14;18)]\)
- cell of origin: germinal center B-cell

- defer treatment if asymptomatic (“watch-and-wait”)
- several chemotherapy options if symptomatic
- median survival: years
- despite “indolent” label, morbidity and mortality can be considerable
- transformation to aggressive lymphoma can occur
**Diffuse large B-cell lymphoma**

- most common type of “aggressive” lymphoma
- usually symptomatic
- extranodal involvement is common
- cell of origin: germinal center B-cell or activated B-cell
- treatment should be offered- R-CHOP is the standard
- curable in ~ 40%

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**Diffuse Large B-Cell Lymphoma (DLCL): OS**

![Graph showing OS rates for different IPI groups](Adapted from Armitage. J Clin Oncol. 1998;16:2780.)

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**Strategies tested to improve the clinical outcome of DLBCL patients**

<table>
<thead>
<tr>
<th>Modality investigated</th>
<th>Improvement in response rate</th>
<th>Improvement in PFS or OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Dense R-CHOP 14 vs. R-CHOP 21 (AMNAS trial)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Increase number of cycles R-CHOP x 6 vs. R-CHOP x 8 (RECOVER)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>High dose chemotherapy and autologous stem cell support (HDCASCT) in first remission for high risk DLBCL (Stiff et al., JCO 2011, #8011)</td>
<td>No Favor in PFS at 2-years (69% vs. 56%, P=0.001)</td>
<td>Study included CHOP and R-CHOP treated patients</td>
</tr>
<tr>
<td>Increasing intensity regimen without HDC-ASCT (R-Mega vs. R-CHOP)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rituximab Maintenance (ECOG 4494 and CORAL studies)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Current areas of research in aggressive B-cell lymphoma

1) Predicting patients that are less likely to respond to rituximab-CHOP in the front-line setting

2) The identification of key-regulatory pathways present in relapsed/refractory DLBCL

3) Can the targeting those pathways translate into clinical benefit?

Gene-expression profiling subdivides morphologically indistinguishable DLBCL tumors into three distinct cell-of-origin (COO) subtypes

Distinct subtypes of DLBCL

<table>
<thead>
<tr>
<th>Molecular subtype</th>
<th>Regimen</th>
<th>3-year PFS</th>
<th>3-year overall survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC DLBCL</td>
<td>RICOHP</td>
<td>40%</td>
<td>Approximately 65%</td>
<td>Lenz et al. (2006)*</td>
</tr>
<tr>
<td>GCB DLBCL</td>
<td>RICOHP</td>
<td>72%</td>
<td>Approximately 80%</td>
<td>Lenz et al. (2006)*</td>
</tr>
<tr>
<td>PB/BL</td>
<td>DA-EPOCH</td>
<td>100%*</td>
<td>97%*</td>
<td>Dohner et al. (2010)*</td>
</tr>
</tbody>
</table>

* PFS = progression-free survival; OS = overall survival.
Hodgkin lymphoma

Thomas Hodgkin (1798-1866)

Classical Hodgkin Lymphoma

- cell of origin: germinal centre B-cell
- Reed-Sternberg cells (or RS variants) in the affected tissues
- most cells in affected lymph node are polyclonal reactive lymphoid cells, not neoplastic cells
- Standard therapy: ABVD
Kaplan-Meier curves for freedom from progression (FFP)/Overall survival and for early (HD7, arm B, 289 patients), intermediate (HD8, 1138 patients), and advanced (HD9, arm C, 466 patients) Hodgkin's lymphoma patients according to the experience of the German Hodgkin's Lymphoma Study Group (GHSG).
Recent advances in preclinical research have resulted in a better understanding of the molecular pathogenesis of lymphomas.

Discover pathways involved in their development and progression.

Several new agents have been developed that specifically inhibit the components of these pathways and which are now in clinical evaluation for lymphomas.
Key signaling pathways implicated in ABC DLBCL

Oncogenic mechanisms and potential targets in DLBCL subtypes

Table 1: Oncogenic mechanisms and potential targets in DLBCL subtypes

<table>
<thead>
<tr>
<th>DLBCL subtype</th>
<th>Cell of origin</th>
<th>Oncogenic mechanisms</th>
<th>Potential targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCs</td>
<td>Germinal centre B cell</td>
<td>BCL6, EZH2 expression&lt;sup&gt;*&lt;/sup&gt;</td>
<td>SYK inhibitors, PI3K inhibitors</td>
</tr>
<tr>
<td>ABC</td>
<td>Post-germinal centre B cell</td>
<td>MYD88&lt;sup&gt;+&lt;/sup&gt; activation, BCR expression&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Enzastaurin, Sotrastaurin</td>
</tr>
<tr>
<td>PBMB</td>
<td>Post-thymic B cell</td>
<td>NFκB&lt;sup&gt;+&lt;/sup&gt; expression, REL amplification, JAK2 mutations</td>
<td>Ibrutinib, Enzastaurin</td>
</tr>
</tbody>
</table>

Advances in monoclonal antibody (mAb) technology have allowed the production of a high number of new mAbs directed against antigens present on the surface of lymphoma cells.

Based on the cell surface antigens they recognize, mAbs can be divided into those directed against:

- B-cell lineage specific antigens (e.g. CD20, CD19, CD22, CD23, CD37)
- Other superficial antigens (not B-cell specific, e.g. CD40, CD80, CD30)

CD19 is a B-cell specific antigen that has been targeted for the treatment of lymphomas. Blinatumomab, a bispecific T-cell engager antibody, is composed of a single-chain bispecific antibody targeting both CD19 and CD3.

Bringing cytotoxic CD3-positive T cells in the proximity of the malignant CD19-positive lymphoma cells to be killed.
CD22 is expressed in 60%–90% of B-cell NHLs, and represents an excellent target for therapy with antibody drug conjugates (ADCs).

Inotuzumab ozogamicin (CMC-544), a CD22 mAb conjugated with the potent chemotherapy agent calicheamicin, resulted in substantial single-agent activity in both indolent and aggressive NHL.

CMC-544 has entered clinical evaluation in combination with rituximab, with salvage chemotherapy regimens and more recently with other targeted agents.

Brentuximab vedotin (SGN35) is an anti-CD30 ADC, already approved.

The PI3K/akt/mTOR pathway: important in several cellular processes including cell proliferation, survival, growth and motility.

- mTOR inhibitors: Temsirolimus and everolimus
- PI3K: The isoform δ (PI3Kδ) has been linked to the development of lymphomas. CAL101
- Histone deacetylase inhibitors: Histone deacetylation is an epigenetic mechanism associated with gene silencing in both haematological and solid tumors. Vorinostat, romidepsin, panobinostat and mocetinostat
What are Chimeric antigen receptors?

Enhanced cytokine production and proliferation

Chimeric Antigen Receptor (CAR) T-Cell Therapy
Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

In vivo expansion and persistence of CTL019

There are far, far better things ahead than any we leave behind.

C.S. Lewis

“The important thing is to never stop questioning.”

Albert Einstein

Questions?