Lymphoma 101: The Basics

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What we hope you will learn today:

• What are lymphomas are why are there so many types?
• How do we diagnose lymphomas and what tests are helpful in diagnosis, staging and classification?
• What are the goals of treatment?
• What are options for classes of treatment?
What are Lymph Cells?

- Your normal blood system has many components
  - Red blood cells
  - Platelets
  - White Blood Cells

- There are many types of White Blood Cells

- Lymphocytes are a form of normal white blood cells involved in regulating the immune system
What are Lymphomas?

- Everyone has lymphocytes: white blood cells which have a role in immune regulation
  - Circulate through the lymphatic system (including >600 lymph nodes) and all organs of the body
- Lymphomas are cancers of the lymphatic system and a component of the immune system
  - A blood cancer
What are Lymphomas?

- Lymphomas occur when these cells learn to grow without infection, inflammation, trauma

- Most often present in lymph nodes but can present in any organ system
  - Gastrointestinal tract
  - Bone/Bone marrow
  - Central Nervous system
  - Liver
Not All Enlarged Lymph Nodes are Lymphoma

- **Infections**
  - Viral infections: EBV (mono), CMV, HIV, Hepatitis
  - Fungal infections: histoplasmosis, cryptococcus
  - Bacterial infections: tuberculosis

- **Autoimmune Conditions**

- **Cancer accounts for 1% of all lymphadenopathy**
  - A very long laundry list!
Lymphomas arise from halt of normal lymphocyte maturation

B-cell Maturation

Harrison’s Principles of Internal Medicine
Lymphomas arise from halt of normal lymphocyte maturation

B-cell Maturation

Infant cells → Leukemia

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B-cell Maturation
Toddler cells → Aggressive Lymphomas

Infant cells → Leukemia

Harrison’s Principles of Internal Medicine
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**B-cell Maturation**

- **Infant cells** → Leukemia
- **Toddler cells** → Aggressive Lymphomas
- **Teenager cells** → Mantle cell Lymphomas
Lymphomas arise from halt of normal lymphocyte maturation

B-cell Maturation

Toddler cells $\rightarrow$ Aggressive Lymphomas

Teenager cells $\rightarrow$ Mantle cell Lymphomas

Adult cells $\rightarrow$ Indolent Lymphomas

Infant cells $\rightarrow$ Leukemia

Washington University Physicians
Department of Medicine
Division of Oncology
Lymphomas arise from halt of normal lymphocyte maturation

**T-cell Maturation**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Differentiation</th>
<th>Thymus</th>
<th>Malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Prothymocyte</td>
<td>CD: 2, 7, 38, 71</td>
<td>Majority of T cell ALL</td>
</tr>
<tr>
<td>II</td>
<td>Thymocyte</td>
<td>CD: 1, 2, 4, 7, 8, 38</td>
<td>Minority of T-ALL, Majority of T-LL</td>
</tr>
<tr>
<td>III</td>
<td>Thymocyte</td>
<td>CD: 2, 3, 4/8, 5, 6, 7, TCR</td>
<td>Minority of T-LL, Rare T-ALL</td>
</tr>
</tbody>
</table>

**Peripheral Blood and Nodes**

- Mature T Helper Cell: CD: 2, 3, 4, 5, 6, 7, TCR
- Mature T Cytotoxic/Suppressor Cell: CD: 2, 3, 4, 5, 6, 7, TCR

Majority of T-CLL, CTCL, Sezary Cell, NHL

Minority of T-CLL, NHL

*Harrison’s Principles of Internal Medicine*
Lymphoma Background

- 15,720 cases per year
  - Incidence increasing ~4%/year
  - 4% of all Cancers in the US

- >90 forms of Lymphoma
Hodgkin Lymphoma

- Characterized by abnormal cells called Reed Sternberg Cells.
- Reed Sternberg Cells only make up 2% of the tumor tissue.
  - Remainder of the tumor is other cells of inflammation.
- Hodgkin lymphoma was the first to be distinguished from other lymphomas.
  - First to be cured with radiation.
  - First to be cured with chemotherapy.

Thomas Hodgkin (1798-1866)
All the rest are non-Hodgkin lymphomas

- >90 Types
- Goals of treatment and treatment options differ on the type
# How I categorize Non-Hodgkin Lymphomas

<table>
<thead>
<tr>
<th>Indolent</th>
<th>Aggressive</th>
<th>VERY Aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>DLBCL</td>
<td>Burkitt</td>
</tr>
<tr>
<td>SLL</td>
<td>Mantle Cell</td>
<td>Lymphoblastic</td>
</tr>
<tr>
<td>Marginal Zone</td>
<td>PTCL</td>
<td>CNS DLBCL</td>
</tr>
<tr>
<td>Mycosis Fungoides</td>
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</table>

**Tx urgency:**
- Weeks/months
- Observation → Oral Therapies → Combination chemotherapy
- Days/Weeks
- Combination chemotherapy
- Hours/Days
- Combination Chemotherapy
Schematic

Lymphomas

Hodgkin

Non-Hodgkin

T-cell

CTCL

PTCL

B-cell

Indolent

Aggressive

Very Aggressive

• CLL
• Follicular
• Marginal Zone

• Mantle cell

• DLBCL

• Burkitt’s
• Plasmablastic

Treatable but not curable → Curable
Signs and Symptoms

- Lymphadenopathy
- Fevers
- Chills
- Drenching night sweats
- Unintentional weight loss
- Fatigue
- Itching/Rash
- Other organ dysfunction

B-symptoms
What kind of lymphoma is it?

- More than 40 subtypes of lymphoma
- **Hodgkin lymphoma (HL)**
- **Non-Hodgkin lymphoma (NHL)**
  - Indolent (slow growing) (e.g. Follicular Lymphoma)
  - Aggressive (rapidly growing) (e.g. Diffuse Large B Cell Lymphoma)
How to Diagnose Lymphomas

- Biopsy!
  - Fine Needle Aspirate
  - Core Needle Biopsy
  - Excisional Biopsy (preferred)

- Immunohistochemistry
- Flow Cytometry
- Cytogenetics
How to Diagnose Lymphomas

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How to Diagnose Lymphomas

• Must be careful to determine that this is a CLONAL process

• Brisk inflammation, response to infections can be confused for lymphoma

• Clonality can be identified through:
  • Immunohistochemistry
  • Flow Cytometry
  • Cytogenetics
  • Molecular Diagnostics
Immunohisotchemistry

- Use an antibody against a protein on the cell
  - Antibody tagged with dye or fluorescence
- Compare number of stained cells to unstained cells on a slide
Flow Cytometry

- Tissue in suspension and tagged with antibodies
- Single cells pass through laser beam that checks for multiple cell proteins at one time
- Can be used to detect whether multiple proteins are co-expressed on the same cell

![Flow cytometry diagram with scatter plots showing CD4+ and CD8+ expression](image-url)
Cytogenetics

- Looking for changes in the chromosomes

- Can be done through a test called FISH (fluorescent in situ hybridization) or traditional cytogenetics

Ventura et al. 2006
Staging: How we know where the Lymphoma Is?

• Scans (Pictures)
  • CT Scan
  • PET/CT Scans
  • Xray
  • MRI

• Bone Marrow Biopsy
Most Lymphomas Use the Ann Arbor System
PET/CT

- Uses radioactively tagged glucose (sugar) to highlight areas of high cell turnover (e.g. cancer, infection, trauma, inflammation)

Before Treatment

After Treatment
Treatment Options

- Chemotherapy
- Radiation Therapy
- Antibody Therapy
- Immunotherapy (boost the immune system to stop the cancer)
- Antibodies attached to chemotherapy
- “Targeted Therapies: Therapies to block key cancer pathways
- Stem Cell Transplant
  - Autologous: From your own cells
  - Allogeneic: Replacing your immune system with someone elses
Treatment Options

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# Treatment Options Are Expanding

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<tbody>
<tr>
<td>Polatuzumab</td>
<td>Duvelisib</td>
<td>Copanlisib</td>
<td>Nivolumab</td>
<td>Belinostat</td>
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<tr>
<td>vedotin</td>
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<tr>
<td>Mogamulizumab</td>
<td>Acalabrutinib</td>
<td>Venetoclax</td>
<td>Blinatumomab</td>
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<tr>
<td></td>
<td>Tisagenleucel</td>
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<td>Siltuximab</td>
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<td></td>
<td>Axicabtagene</td>
<td></td>
<td>Idelalisib</td>
<td></td>
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<tr>
<td></td>
<td>Pembrolizumab</td>
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How Do We Decide Which Treatment To Do?

- Sub-type of lymphoma
- Stage of lymphoma
- Site of lymphoma involvement (CNS involvement – needs additional chemo)
- Age and other health problems (Special drug toxicities)
- Convenience and Logistics
- New: use of genetic markers
Chemotherapy

• Medicines that help kill dividing cells
• Take advantage of the fact that lymphoma cells divide faster than normal cells
• Many types of chemotherapy that each have unique side effects
• Often part of curative treatment in initial treatment of lymphoma

• Side effects result from damage to normal cells that are dividing
  • GI Tract
  • Hair
  • Blood System
Radiation Therapy

• Also causes death to dividing cells
• Usually used as local therapy in lymphoma (treat one spot)
• Can have side effects if radiation affects other normal structures in the way
Antibody Therapy

- Develop protein (antibody) that recognizes a protein on the cancer cell
- Your immune system recognizes the antibody and tries to eliminate the cell attached to it
- Example: Rituximab (against CD20)
Antibody Drug Conjugates

- Attaches chemotherapy to an antibody that recognizes a cancer protein.
- Delivers chemotherapy to the cancer with less side effects.
- Example: Brentuximab vedotin in T-cell lymphoma or Hodgkin lymphoma.

Younes A et al. NEJM 2010

ADC binds to CD30
ADC-CD30 complex traffics to lysosome
MMAE is released
MMAE disrupts microtubule network

Monomethyl auristatin E (MMAE), potent antitubulin agent
Protease-cleavable linker
Anti-CD30 monoclonal antibody
Immunotherapy

- Tumor cells are have elements of your own body and elements unlike your normal body

- Tumor cells can disguise from the immune system using proteins that help them prevent the immune system from affecting them

Immunotherapy/Checkpoint Inhibitors

- Normal immune systems have “breaks” and “accelerators” to modulate the immune system
- Checkpoint inhibitors take the breaks off the immune system and uncloaks the disguised cancer
- Examples: Nivolumab or Pembrolizumab for Hodgkin lymphoma

Targeted Therapy

- Cancer cells grow through multiple simultaneous mechanisms
- Targeted therapy stops proteins that help the cancer cells grow
Chimeric Antigen T-cells

1. IN THE CLINIC
   The white blood cells, including T cells, are separated out, and the rest of the blood is returned to the patient.

2. IN THE LAB/MANUFACTURING FACILITY
   T cells are engineered to find and kill cancer cells.
   - An inactive virus is used to insert genes into the T cells.
   - The genes cause the T cells to make special receptors, called CARs, on their surfaces.
   - Modified T cells (now called CART cells) are multiplied until there are millions of these attacker cells.

3. IN THE CLINIC
   CART cells are put back into the patient's bloodstream, typically after chemotherapy is given to make space, and continue to multiply.

4. IN THE BODY
   - The receptors are attracted to targets on the surface of the cancer cells.
   - The CART cells identify the cancer cells with the target antigens, and kill them. CART cells may remain in the body for some time to help prevent the cancer cells from returning.
How Did I Get Lymphoma?

• Most lymphomas originate by a mistake in the normal replication of the lymph cells

• There’s usually nothing a patient did or didn’t do that caused lymphoma
Will my kids get lymphoma?

• Most forms of lymphoma are not hereditary
What Can I Do to Advocate for Myself and Others?

• Be Informed
  • The Lymphoma Research Foundation has fantastic resources
• Talk to others about your lymphoma
• Consider clinical trials
• Support Research
• Be active in the community, support groups
Thank you!

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