Indolent Lymphomas: Current

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MUHC
Why does indolent mean?

- Slow growth
- Often asymptomatic
- Chronic disease with periods of relapse (long natural history possible)
- Incurable with current standard therapy, but long remissions possible
- Goal of treatment is to maximize quality of life
## Indolent lymphomas

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>3.4</td>
</tr>
<tr>
<td>Marginal zone or MALT</td>
<td>1.8</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>0.4</td>
</tr>
<tr>
<td>Waldenstrom’s macroglobulinemia</td>
<td>0.3</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>0.3</td>
</tr>
<tr>
<td>Primary cutaneous</td>
<td>0.1</td>
</tr>
</tbody>
</table>

SEER Database Incidence 2011-12
Lymphocytes

• **B cells** develop in the bone marrow
  • form antibodies against foreign bodies
    ➢ 90% of all lymphomas

• **T cells** mature in the thymus gland
  • orchestrate the immune response
    ➢ 10% of lymphomas

• **NK (natural killer) cells**
  • destroy viruses and cancers through direct attack
    ➢ Very rare lymphomas, rarely indolent
How do we figure out which type you have?

- **Physical Exam**
  - Cardiac, respiratory, abdominal
  - Lymph nodes

- **Biopsy**
  - FNA or core biopsy
  - Incisional biopsy
  - Excisional biopsy

- **Laboratory**
  - CBC and differential
  - LDH (prognostic marker in NHL)
  - ESR (important in HL)
  - Bone marrow aspirate/biopsy

- **Imaging**
  - Chest X-ray
  - Ultrasound
  - CT scan neck/ chest/ abdomen/pelvis
  - Gallium Scan
  - PET

- **Other**
  - LP – if CNS symptoms, or in certain high risk cases of aggressive lymphoma (sinus, testicle, bone marrow)
Biopsies
Why is pathology important?

• Need to determine the most appropriate therapy

• Some of the criteria for diagnosis are very specific—and lead to specific treatment choices
  For example:
  • CD20 “positive” by immunohistochemistry: use of rituximab

• May provide prognostic information
Pathology and molecular analysis

- Morphology
- Immunohistochemistry
- Cytogenetics
- Gene expression profiling
Staging

The # of staging investigations is dependent on the type of lymphoma and goals of therapy.

Staging is used to determine:
- Extent of disease
- Bulk of tumour mass
- Potential for complications
- Type of treatment
Ann Arbor Staging System

Stage I

Stage II

Stage III

Stage IV

A – absence of any “B” symptoms

B – unexplained fever, drenching sweats or weight loss

Bulky > 10 cm mass on imaging

E – extranodal involvement
International Prognostic Index (IPI)

Evaluates 5 variables:

- Age
- Stage
- Performance status: what is the impact of lymphoma (or other medical problems) on daily life – how sick are you?
- Number of extranodal sites
- LDH
Follicular lymphoma

- Typically affects middle-aged and older adults
- Abnormal follicles give disease its name
- Causes few symptoms in early stages
- Usually responds well to treatment, but can return
- Can transform into aggressive lymphoma
## FLIPI- Follicular Lymphoma International Prognostic Index

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adverse factor</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>$\geq 60,\text{y}$</td>
<td>2.38</td>
<td>2.04-2.78</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td>III-IV</td>
<td>2.00</td>
<td>1.56-2.58</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>$&lt; 120,\text{g/L}$</td>
<td>1.55</td>
<td>1.30-1.88</td>
</tr>
<tr>
<td>Serum LDH level</td>
<td>$&gt; \text{ULN}$</td>
<td>1.50</td>
<td>1.27-1.77</td>
</tr>
<tr>
<td>Number of nodal sites</td>
<td>$&gt; 4$</td>
<td>1.39</td>
<td>1.18-1.64</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Prognosis</th>
<th>% Patients</th>
<th>OS (10 yr)</th>
</tr>
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<tbody>
<tr>
<td>0-1</td>
<td>good</td>
<td>36</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>moderate</td>
<td>37</td>
<td>51</td>
</tr>
<tr>
<td>3-5</td>
<td>poor</td>
<td>27</td>
<td>36</td>
</tr>
</tbody>
</table>
Marginal zone lymphoma

- Accounts for ~10% of NHL
- Affects older adults usually
- 3 types:
  - **Extranodal marginal zone lymphoma or mucosa-associated lymphoid tissue (MALT)**
    - Occurs outside the lymph nodes, for example in the stomach, small intestine, salivary glands, thyroid, eyes or lungs
  - **Nodal marginal zone lymphoma**
    - Occurs within lymph nodes
  - **Splenic marginal zone lymphoma**
    - Usually occurs in spleen and blood
Waldenstrom’s macroglobulinemia

- Dr. Jan Waldenstrom first described the condition in 1948
- Rare, 1-2% of NHLs, usually affecting older adults
- Primarily found in bone marrow
- Overproduction of IgM protein, causing thickening of blood
- Plasmapheresis may temporarily reverse or prevent symptoms associated with blood thickening.
Hairy cell leukemia

• Surface of cells look hairy under microscope
• Called ‘leukemia’ as cancerous lymphocytes can be found in the blood, though they mainly collect in the bone marrow and spleen
• Rare subtype usually found in middle-aged or older adults
Cutaneous lymphoma

- Lymphoma in the skin
- Usually T cell, but can be B cell
- Most common subtype: mycosis fungoides
- Most common in those aged 50+, but can occur in younger adults
- Often small, raised, red patches on skin that may look like eczema or psoriasis
- Ulcerating tumours (open sores) can appear
- Treatment may include ultraviolet light
Watch & wait

Randomized trial of “Watch and Wait” vs. early chemotherapy
British National Lymphoma Investigation Trial of 309 patients with indolent NHL

<table>
<thead>
<tr>
<th>Results</th>
<th>“Watch and Wait”</th>
<th>Early chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma-specific survival</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>No difference</td>
<td></td>
</tr>
</tbody>
</table>

- On average, patients needed treatment ~2.5 years from diagnosis
- However, 1 in 5 participants did not require treatment by 10 years
- 2 in 5 over the age of 70 did not require treatment
Coping with watch & wait

• Be gentle with yourself
• Talk it out
• Take care of yourself (healthy living)
• Learn about lymphoma (dispelling the myths)
• Ask for support
Indications for starting treatment

- Symptoms attributable to the lymphoma
- Low blood counts because of bone marrow involvement
- Threat to organ function
- Bulky disease or spleen
- Disease that has transformed to an aggressive lymphoma
# Overview of primary treatment options

<table>
<thead>
<tr>
<th>Treatment Option</th>
<th>Description</th>
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<tbody>
<tr>
<td>Chemotherapy</td>
<td>Use of drugs to kill lymphoma cells</td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>Use of high-energy rays to kill lymphoma cells or slow their growth</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Use of agents designed to target and destroy lymphoma cells</td>
</tr>
<tr>
<td>Transplantation</td>
<td>Infusion of healthy stem cells/bone marrow after high dose chemotherapy, to help the body restore its supply of healthy blood cells</td>
</tr>
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**Balance potential toxicity against effectiveness**
Chemotherapy

- Backbone of many cancer treatments
- Damages DNA, leading to cell death
- Systemic
- Affects all growing cells
  - Cancer cells
  - Blood cells
  - Lining of GI tract
  - Hair
Common chemotherapy regimens

**CHOP** - with or without R (Rituxan)
- Cyclophosphamide
- Doxorubicin
- Vincristine
- Prednisone— pills daily x 5 days

By IV every 3 weeks

4 cycles—if radiation is also part of the plan
6 cycles—most often
8 cycles—in some circumstances
Common chemotherapy regimens

CVP – with or without R
- Cyclophosphamide
- Vincristine
- Prednisone — pills daily x 5 days

By IV every 3 weeks

For a usual total of 6 to 8 cycles unless disease progression or unacceptable toxicity occurs
Common chemotherapy regimens

**Single Agents**, with or without R

**Bendamustine**
- Infuse on days 1 & 2
- By IV every 4 weeks
- Maximum 6 cycles

**Chlorambucil**
- Pill
- Dosage varies

**Fludarabine**
- Pill or IV for 5 days
- Repeat every 4 weeks
- Maximum 8 cycles

**Cladribine**
- IV for 5 days
Immunotherapy

- Also called biologic therapy
- Drugs designed to boost the body’s natural defenses against cancer
- Generally fewer side effects than traditional chemotherapy
Monoclonal antibodies

Antibodies developed against cancer cells can be administered to patients to destroy the tumour

- Examples:
  - Rituximab
  - Obinutuzumab

*Only work for lymphomas that express the target protein*

Why add rituximab?

Addition of anti-CD20 antibody rituximab to chemotherapy: improvement in survival.

Hiddemann et al. Blood, 2005

R-CHOP: 6 deaths (n = 225)
CHOP: 17 deaths (n = 203)

$p = 0.016$
Rituximab maintenance

- Rituximab maintenance for 2 years
- Administered every 2 months, 12 cycles

Targeted therapies

Drugs that target specific molecules on the surface of cancer cells or cell pathways.

Ibrutinib

• Pill, taken as directed until disease progression or intolerance to drug develops

Idelalisib

• Pill, taken alone or in combination with Rituximab, until progression or intolerance
Radiation

Medical uses of radiation:

1. Diagnostic: low doses of radiation to take images of internal body structure i.e. chest X-ray
2. Therapeutic: higher doses of radiation to kill cancer cells

Difference between the two is the amount of energy. Therapeutic radiation can use up to 1,000 times the energy of diagnostic radiation.
Radiation

- X-ray beams interact with atoms, creating a reaction that leads to cell DNA damage
- Damage prevents the cells from dividing and growing
- Lymphocytes are the most sensitive cells in the body to radiation, so can use lower doses of radiation compared to what is used to treat solid tumours.
Radiation

Linear Accelerators

• Machines do not use radioactive sources but instead use electricity to produce X-rays and electrons.

• Versatile as they can produce different energies of radiation, to minimize the normal tissue affected.
Radiation

• Applies to localized disease
• May not be used in all types of indolent NHL
• Generally treatment is given daily for 4 weeks (Monday to Friday X 4 weeks = 20 treatments or “fractions”)
• Side effects based on the area that is being radiated (skin and tissue beneath it)
Common radiation fields

- Mantle
- Abdominal
- Pelvic
Combination therapy

- Chemotherapy + radiation
- Chemotherapy + immunotherapy = chemoimmunotherapy
- Radiation (radioactive isotopes) + immunotherapy = radioimmunotherapy

Monoclonal antibody alone

With radioactive isotopes
Side effects of treatment

Short term:
• Hair loss
• Mouth sores
• Nausea, vomiting: controllable with medication
• Fatigue
• Fever: need a thermometer! If > 38.3 or 101.5º get a blood test (even Sunday afternoon...)
• Low blood counts
Other possible issues

• Heart function: may need monitoring
• Peripheral neuropathy (numb hands, feet)
• Difficulty with memory, concentration (multi-tasking)—“chemobrain”
• Fertility
Other possible issues

• Secondary cancers
• Work/school
• Going out in public, infection risks
• Immunization
Stem cell transplant (SCT)

**Autologous**
- Use own cells
- Low treatment related mortality
- High rates of remission
- Transplant strategies vary centre-to-centre
Stem cell transplant (SCT)

Allogeneic

- Rare
- HLA matched sibling or matched unrelated donor
- 1 in 4 chance of sibling being a match
- Graft versus lymphoma: good!
- Graft versus host disease: can be very bad, including fatal, and life long
- Higher treatment related mortality
After treatment is completed

• Repeat staging tests to determine if the lymphoma is “in remission”
  ➢ Hope that we have attained a long period of disease control before we have to re-treat the lymphoma

• Follow-up with your family MD (~annually)
  ➢ Screening for secondary cancers
  ➢ Vaccines

• Follow-up with your oncologist (~3 months)
Relapse/refractory

- Many other treatments available
- Goals of therapy may change
- Clarification of goals with your oncologist is very important
- Clinical trials of new agents