Indolent Lymphoid Disorders
Lazy nothingness or incurable lethality?

Michael Tees, MD, MPH
Hematology ~ Blood and Marrow Therapies
Colorado Blood Cancer Institute
Objectives

Identify that indolent lymphomas should be considered indolent lymphoid disorders

Understand the mortality implications of the indolent lymphoid disorders depending on age, treatment, and other prognostic factors

Understand the long-term outcomes after hematopoietic cell transplantation
Indolent Lymphoid Disorders

Review

What is indolent?

Disease management and implications

Survival and factors affecting mortality
Indolent Lymphoid Disorders

Review

What is indolent?

Disease management and implications

Survival and factors affecting mortality
## Hematologic Malignancies

<table>
<thead>
<tr>
<th>Hematologic Disease</th>
<th>US Incidence, 2015 estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>162,020</td>
</tr>
<tr>
<td><strong>Myeloid</strong></td>
<td></td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>20,830</td>
</tr>
<tr>
<td>Chronic Myeloid Leukemia</td>
<td>6,660</td>
</tr>
<tr>
<td><strong>Plasma Cell</strong></td>
<td>26,850</td>
</tr>
<tr>
<td><strong>Lymphoid</strong></td>
<td></td>
</tr>
<tr>
<td>Acute Lymphocytic Leukemia</td>
<td>6,250</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>9,050</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>71,850</td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia</td>
<td>14,620</td>
</tr>
</tbody>
</table>

*Source: American Cancer Society, 2015*
Hematopoiesis

HSC

Myeloid

Lymphoid

B T

NK
Indolent Lymphoid Disorders

Review
What is indolent?
Disease management and implications
Survival and factors affecting mortality
Hematologic Malignancies

<table>
<thead>
<tr>
<th>Hematologic Disease</th>
<th>US Incidence, 2015 estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>162,020</td>
</tr>
<tr>
<td><strong>Myeloid</strong></td>
<td></td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>20,830</td>
</tr>
<tr>
<td>Chronic Myeloid Leukemia</td>
<td>6,660</td>
</tr>
<tr>
<td><strong>Plasma Cell</strong></td>
<td>26,850</td>
</tr>
<tr>
<td><strong>Lymphoid</strong></td>
<td></td>
</tr>
<tr>
<td>Acute Lymphocytic Leukemia</td>
<td>6,250</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>9,050</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>71,850</td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia</td>
<td>14,620</td>
</tr>
</tbody>
</table>

Source: American Cancer Society, 2015
Lymphoid Disorders

B-cell disorders: \( \sim 90\% \)

T-cell disorders: \( \sim 10\% \)

NK-cell disorders: \( \sim 1-2\% \)
Indolent Lymphoid Disorders

**Indolent:**
1a: causing little or no pain
1b: slow to develop or heal

2a: averse to activity, effort or movement
2b: conducive to or encouraging laziness

Source: Mirriam-Webster Dictionary
Classic Thought

Indolent = incurable

Aggressive = potentially curable
Classic Thought

Indolent: risk of progression

Aggressive: risk of relapse after treatment
Classic Action

Indolent = Watch and Wait

Aggressive = Treat now!
Lymphoid Disorders

Aggressive:
DLBCL
Mediastinal Large B-cell Lymphoma
Primary Effusion Lymphoma
Hodgkin Lymphoma*
Burkitt Lymphoma
Peripheral T-cell Lymphoma
NK cell Leukemia

Mantle Cell Lymphoma
Hairy Cell Leukemia
Lymphoid Disorders

Aggressive:
DLBCL
Mediastinal Large B-cell Lymphoma
Primary Effusion Lymphoma
Hodgkin Lymphoma*
Burkitt Lymphoma
Peripheral T-cell Lymphoma
NK cell Leukemia

Mantle Cell Lymphoma
Hairy Cell Leukemia

TREAT NOW!
Lymphoid Disorders

**Indolent:**
- Follicular Lymphoma
- Marginal Zone Lymphomas
- Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Lymphoplasmacytic Lymphoma/Waldenstrom’s Macroglobulinemia
- * Nodular Lymphocyte-Predominant Hodgkin Lymphoma
- Primary Cutaneous Lymphoproliferative Disorders
- T-cell Large Granular Lymphocytic Leukemia (T-LGLL)
- Cutaneous T-Cell Lymphoma (Mycosis Fungoides/Sezary Syndrome)
Lymphoid Disorders

**Indolent:**
Follicular Lymphoma
Marginal Zone Lymphomas
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Lymphoplasmacytic Lymphoma/Waldenstrom’s Macroglobulinemia
* Nodular Lymphocyte-Predominant Hodgkin Lymphoma
Primary Cutaneous Lymphoproliferative Disorders
T-cell Large Granular Lymphocytic Leukemia (T-LGLL)
Cutaneous T-Cell Lymphoma (Mycosis Fungoides/Sezary Syndrome)

**WATCH AND WAIT**
Lymphoid Disorders

**Indolent:**
- Follicular Lymphoma
- Marginal Zone Lymphomas
- Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Lymphoplasmacytic Lymphoma/Waldenstrom’s Macroglobulinemia
- *Nodular Lymphocyte-predominant Hodgkin Lymphoma*
- Primary Cutaneous Lymphoproliferative Disorders
- T-cell Large Granular Lymphocytic Leukemia (T-LGLL)
- Cutaneous T-Cell Lymphoma (Mycosis Fungoides/Sezary Syndrome)

**WATCH AND WAIT FOR WHAT?**

---

**CBCI**
COLORADO BLOOD CANCER INSTITUTE
Indolent Lymphoid Disorders

Review

What is indolent?

Disease management and implications

Survival and factors affecting mortality
Current Management

Aggressive

Indolent

Lymphoid

NK

B

t

Cancer Institute
Indolent Lymphoid Disorders

How we decide to treat:

 Symptoms or disease burden

Molecular/genetic determinants

Prognostication (FLIPI, MIPI, IPI, Rai)
Follicular Lymphoma

**FLIPI-2 Score**

- Age > 60
- Hgb < 12
- Bone marrow involvement
- beta-2 microglobulin elevated
- Longest diameter of largest LN > 6cm

Score 3-5 = approx 50-60% OS at 5 years

*Source: Federico et al, J Clin Oncol 2009*

**Pathologic grading of disease (grade 1-2 vs 3)**
Follicular Lymphoma: GELF Criteria

- Involvement of ≥3 nodal sites, each with a diameter of ≥3 cm
- Any nodal or extranodal tumor mass with a diameter of ≥7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes <1.0 x 10^9/L and/or platelets <100 x 10^9/L)
- Leukemia (>5.0 x 10^9/L malignant cells)
(A) Progression-free survival (PFS) and (B) overall survival (OS) of the training sample (832 patients) according to the Follicular Lymphoma International Prognostic Index 2 (FLIPI2); (C) PFS and (D) OS of the validation sample (231 patients) according to F...
Lymphoplasmacytic Lymphoma

- Hyperviscosity
- Neuropathy
- Organomegaly
- Amyloidosis
- Cold Agglutinin Disease
- Cryoglobulinemia
- Cytopenias due to Disease
- Bulky Adenopathy
LGL Leukemia

Symptoms from autoimmune manifestations

Neutropenia with absolute neutrophil count < 500 or ANC > 500 with chronic infections

Transfusion dependent

CLL/SLL

Age and functional status

Rai/Binet staging

Co-morbidities

FISH/cytogenetics (11q, 17p)

Treatments of Choice

When watching and waiting is over...
Treatments of Choice

**Follicular Lymphoma:**
- CHOP-R (cyclophosphamide, vincristine, doxorubicin, prednisone, rituximab)
- BR (bendamustine, rituximab)
- R (rituximab)
- Radiation Therapy

**Marginal Zone Lymphoma:**
similar to above
Treatments of Choice

Lymphoplasmacytic Lymphoma/Waldenstrom’s Macroglobulinemia:
- Bortezomib +/- rituximab +/- prednisone
- CHOP-R (Cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)
- Ibrutinib

Primary Cutaneous Lymphoproliferative Disorders (CD30+ Anaplastic Large Cell Lymphoma, Lymphomatoid Papulosis):
- Surgical Excision and/or Radiation Therapy
- Methotrexate
- Pralatrexate
- Brentuximab vedotin
- CHOP or CHOEP (in ALCL with regional lymph nodes)
- Phototherapy (Lymphomatoid papulosis)
Treatments of Choice

Nodular Lymphocyte-predominant Hodgkin Lymphoma:
- Radiation Therapy
- Radiation + ABVD*(doxorubicin, bleomycin, vincristine, dacarbazine)
- Radiation + CHOP +/- R (cyclophosphamide, vincristine, doxorubicin, prednisone, rituximab)
- Radiation + CVP +/- R (cyclophosphamide, vincristine, prednisone, rituxumab)

T-cell LGLL:
- Methotrexate +/- corticosteroids
- Cyclophosphamide +/- corticosteroids
- Cyclosporine

Treatments of Choice

**Cutaneous T-Cell Lymphomas (Mycosis Fungoides/Sezary Syndrome)**
- Topical steroids, chemotherapy, imiquimod, or retinoids
- Local radiation
- Phototherapy
- Total skin electron beam therapy

**CLL/SLL:**
- Chlorambucil + obinutuzumab/ofatumumab/rituximab
- Bendamustine + rituximab
- Fludarabine + rituximab
- FCR (fludarabine, cyclophosphamide, rituximab)
- PCR (pentostatin, cyclophosphamide, rituximab)
Treatments of Choice

More on CLL/SLL

17p deletion is a marker of more aggressive disease. Treatment upfront is recommended. This type does not respond as well to chemotherapy/immunotherapy, however, it remains a first-line recommendation. Now:

**Ibrutinib**: Bruton tyrosine kinase (BTK) inhibitor GAME CHANGER

**Idelalisib**: PI3 kinase (PI3K) inhibitor GAME CHANGER

BTK and PI3K inhibitors appear to negate the poor prognosis of del(17p)
Treatment Principles

Rituximab has prolonged overall survival when used in combination with other chemotherapeutic agents.

Then should we use rituximab early and not watch and wait?

Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial

Kaplan-Meier curves for the 252 patients randomly assigned in the initial three-arm study:
(A) Time to start of new treatment, (B) progression-free survival, (C) overall survival, and (D) time to histological transformation. HR=hazard ratio.

After chemotherapy is initiated, rituximab maintenance is often used to prolong disease control.
Treatment: when to transplant

Autologous Hematopoietic Cell Transplant

vs

Allogeneic Hematopoietic Cell Transplant
Treatment: when to transplant

Autologous Hematopoietic Cell Transplant vs Allogeneic Hematopoietic Cell Transplant
Treatment: when to transplant

In follicular lymphoma, if a patient has recurrence of disease within 12-24 months, autologous stem cell transplant is recommended.

If a patient fails an autologous HCT, an allogeneic HCT is indicated.

Treatment: when to transplant

What about the other indolents when disease has progressed?
Treatment: when to transplant

Follicular Lymphoma: AUTO or ALLO
Marginal Zone Lymphomas: AUTO or ALLO
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: ALLO
Lymphoplasmacytic Lymphoma/Waldenstrom’s Macroglobulinemia: AUTO or ALLO
Nodular Lymphocyte predominant Hodgkin Lymphoma: ALLO
Primary Cutaneous Lymphoproliferative Disorders: AUTO or ALLO
T-cell Large Granular Lymphocytic Leukemia (T-LGLL): ALLO
Cutaneous T-Cell Lymphoma (Mycosis Fungoides/Sezary Syndrome): ALLO
Indolent Lymphoid Disorders

Review

What is indolent?

Disease management and implications

Survival and factors affecting mortality
Mortality and Indolent Lymphoid Disorders: a perspective

Even in elderly with FL (> 80 years old in US), OS at 5 yrs is 59%, and only 38% of the deaths were from lymphoma.

Anthracyclines are often removed from these treatments.

Mortality and Indolent Lymphoid Disorders

Common Risk Factors

Treatment-related complications and late effects

Transformation
Common Risk Factors

Most prognostic utilities identify age 60 and older as a risk factor for poorer outcomes - the value of prognostic tools is that it combines risk. Age in of itself may not be a risk factor, but is associated with inferior outcomes.

Time to Progression
Time to Progression

Relapse/Progression by itself is not a good marker of prognosis.

The time to progression may be a better tool.
Risk of Treatment(s)

The indolent nature of the disease = monitoring, treatment, monitoring, treatment...
Risk of Treatment(s)

Transplant Outcomes: Follicular Lymphoma

Late Effects of Therapy

Late toxicities are clinically relevant today.

In the future, targeted therapy may remove some of the secondary effects of therapy.
Late Effects of Therapy

Radiation Therapy

Immunotherapy

Chemotherapy
Late Effects of Therapy

Radiation Therapy:
- location-specific
- may increase risk of breast cancer or cardiomyopathy if administered to the chest/mediastinal region
- in general, this risk is less now with more precise technology

Immunotherapy:
- PML
Late Effects of Therapy

Chemotherapy:

Cardiac:
- Anthracyclines: 5-10%

Pulmonary:
- Bleomycin (in treatment of HL) 18%, median 5 yrs OS 63% vs 90% in those who did not develop

Late Effects of Therapy

Secondary malignancies:

– associated with total dose exposure
– ALL LYMPHOMAS: 15 year cumulative risk 11.2% (< 50 yrs old 7%, > 50 yrs old 17.5%)
- risk plateaus at around 15 yrs from diagnosis

Late Effects of Transplant

Autologous:

- little long-term morbidity/mortality associated with regimens
  – complications can occur (acute kidney injury, arrhythmias)
  – risk of mortality attributed to transplant is approximately 1%
Survival after autologous transplants for follicular lymphoma, 2002-2012

Available at CIBMTR.org

Survival after autologous transplants for mantle cell lymphoma, 2002-2012

Available at CIBMTR.org

Causes of Death after Autologous Transplants done in 2011-2012

Available at CIBMTR.org

Late Effects of Transplant

Allogeneic:

- little morbidity/mortality associated with conditioning regimens itself, less total body irradiation is being used
- cardiovascular disease 10+ years post-transplant
- Pulmonary (idiopathic pneumonia syndrome, bronchiolitis obliterans)
- Skeletal events (avascular necrosis)
- GVHD
- many others...
Late Effects of Transplant

Allogeneic:
- Classify as either relapse mortality and non-relapse mortality
- Unfortunately, non-relapse mortality is often used synonymously with transplant-related mortality
- Mortality within first year is affected by MANY variables
Survival after allogeneic transplants for follicular lymphoma, 2002-2012

Available at CIBMTR.org

Survival after allogeneic transplants for CLL, 2002-2012

Available at CIBMTR.org

Causes of Death after HLA Match Sibling Transplants done in 2011-2012

Available at CIBMTR.org

Causes of Death after HLA Unrelated Donor Transplants done in 2011-2012

Available at CIBMTR.org

Transformation

All indolent lymphomas carry a risk of histologic transformation to an aggressive lymphoma.

Follicular lymphoma, Marginal Zone Lymphoma, CLL have risk to transform to Diffuse Large B-cell Lymphoma.

Nodular Lymphocyte-predominant Hodgkin Lymphoma has a risk to transform to aggressive Hodgkin Lymphoma.

However, transformation can be any which way (FL -> Burkitt Lymphoma, CLL/SLL -> Hodgkin Lymphoma).
Transformation

It is unclear if the risk of histologic transformation is already present and detectable at the time of diagnosis

# Transformation: Incidence

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular Lymphoma</td>
<td>20% at 5yrs</td>
</tr>
<tr>
<td></td>
<td>30% at 10yrs</td>
</tr>
<tr>
<td>CLL</td>
<td>16.2% at 10yrs</td>
</tr>
<tr>
<td>Lymphoplasmcytic Lymphoma</td>
<td>10% at 7yrs</td>
</tr>
<tr>
<td>All Indolent Lymphoid Disorders</td>
<td>14% at 5yrs</td>
</tr>
<tr>
<td></td>
<td>21% at 10yrs</td>
</tr>
<tr>
<td></td>
<td>39% at 15yrs</td>
</tr>
</tbody>
</table>

Approximate 3% annual risk of transformation

Transformation

When patients transform, his/her survival, despite prior therapies, appears to match patients with de novo aggressive lymphomas.

Summary
The indolent lymphoid disorders can be both lazy and lethal

Indolent Lymphomas = Indolent Disorders

It is treatable and possibly curable

Our treatments pose mild risk of toxicity
Indolent

Thank You

Michael Tees, MD, MPH

michael.tees@healthONEcares.com