Disclosures

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  • Abbvie, Celgene, Novartis, Pharmacyclics, Seattle Genetics

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  • BMS, Janssen, Novartis, Takeda, BioInvent, Atara, Seattle Genetics, LAM

• I have received grant funding from ASH and LRF
Outline – Spectrum of indolent NHL lifespan

Long-term Toxicities
Diagnosis and Staging
Quality of Life and Palliative Care
Relapse and Progression
Watchful Waiting
Surveillance
Toxicity Management
Chronic Oral Therapy
Chemoimmunotherapy
Relapse and Progression

Indolent non-Hodgkin Lymphoma(s)

Jaffe, WHO 2008
Clinical Behavior of Indolent Lymphomas

There are many common features of indolent lymphomas

<table>
<thead>
<tr>
<th>Positives</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequently non-aggressive</td>
<td>Considered “incurable”</td>
</tr>
<tr>
<td>Limited symptoms</td>
<td>Long course of treatments</td>
</tr>
<tr>
<td>Good prognosis</td>
<td>Challenging to explain to others</td>
</tr>
<tr>
<td>Many effective therapies (including oral)</td>
<td>Frequently require repeated treatments</td>
</tr>
<tr>
<td>May not require treatment upfront</td>
<td></td>
</tr>
</tbody>
</table>

How is it Diagnosed?

- Many patients have no symptoms
  - Progressive swelling
  - Incidental finding (looking for something else)
  - Routine physical
- Others can have symptoms
  - Unexplained fevers
  - Drenching sweats
  - Weight loss
  - Fatigue?
  - Others depending on site of disease
Making the Correct Diagnosis

- **Excisional biopsy** (surgically removing the lymph node) is preferred whenever possible.
  - Some forms of indolent NHL can’t be biopsied this way (CLL, MALT, others)
- Hematopathology review is important

![Image of lymph node architecture]

Lymph node architecture is critical to making diagnosis

Making the Correct Diagnosis

- Each subtype has a specific signature and/or genetic characteristic
- These help make the diagnosis and can be prognostic

<table>
<thead>
<tr>
<th></th>
<th>Follicular lymphoma</th>
<th>Marginal zone lymphoma</th>
<th>CLL/SLL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunophenotype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD20</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD5</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD10</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Genetic Rearrangement</strong></td>
<td>t(14;18)</td>
<td>t(11;18) - sometimes</td>
<td>Varied</td>
</tr>
</tbody>
</table>
Evaluation of a Newly Diagnosed Patient

- Critical to make the right diagnosis
- CT scan (sometimes PET/CT)
- Appropriate prognostic evaluation
- HIV and Hepatitis Assessment
- Bone marrow biopsy (sometimes)
- Other assessments as indicated

Next steps: Discussion with your team about the diagnosis, stage, prognosis, and appropriate treatment

Things to discuss with your oncologist

- Lymphoma subtype and stage
- General prognosis
- Your symptoms
- Why you may/may not need treatment right away
- Other medical conditions
- Life events
- Quality of life priorities
- Is there a clinical trial option?
You may not need immediate therapy

Decision to start treatment requires a discussion with your physician

<table>
<thead>
<tr>
<th>GELF Criteria for Follicular Lymphoma</th>
<th>iwCLL Criteria for CLL/SLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest mass &lt; 7cm</td>
<td>Anemia or low platelets</td>
</tr>
<tr>
<td>≤ 3 sites with diameter &gt; 3cm</td>
<td>Enlarged spleen</td>
</tr>
<tr>
<td>Limited lymphoma cells in blood</td>
<td>Massive lymph nodes</td>
</tr>
<tr>
<td>Normal blood counts</td>
<td>Rapid doubling time of WBC count</td>
</tr>
<tr>
<td>No fluid collections</td>
<td>Disease-related symptoms</td>
</tr>
<tr>
<td>No organ damage or risked organ damage</td>
<td></td>
</tr>
<tr>
<td>No major spleen enlargement</td>
<td></td>
</tr>
</tbody>
</table>

Solal-Celigny, NEJM, 1993

****There is NO absolute WBC cutoff that requires Treatment in CLL****

Treating Follicular Lymphoma

• There are many options for your first treatment of follicular lymphoma
  • Is chemotherapy required?
  • Which chemotherapy?
  • Which antibody?
  • Is radiation appropriate and/or necessary?
  • What about maintenance?

• Essential to consider your goals, expected prognosis, other medical conditions, lifestyle, and overall disease-related expectations when choosing treatment.
Targeting CD20: The GALLIUM Study

Marcus et al, *NEJM* 2017

Winship Cancer Institute | Emory University
Which chemotherapy is best? The StiL Study

Mantle cell lymphoma and iNHL, including:
- Follicular lymphoma
- Lymphoplasmacytic lymphoma
- Small lymphocytic lymphoma
- Marginal zone lymphoma

1:1

BR
- Bendamustine 90 mg/m² day 1 + 2
- Rituximab 375 mg/m² day 1

R-CHOP
- Cyclophosphamide 750 mg/m² day 1
- Doxorubicin 50 mg/m² day 1
- Vincristine 1.4 mg/m² day 1
- Prednisone 100 mg days 1-5
- Rituximab 375 mg/m² day 1

The StiL Study

Rummel, Lancet, 2013
Side Effects

### CD20 Antibodies (Rituximab/Obinutuzumab)
- Infusion Reaction
- Low antibody levels / recurrent infection
- Rare neurologic complications
- Low blood counts (worse with obinutuzumab)

Side effects are different for every patient and not always predictable.

<table>
<thead>
<tr>
<th>CHOP</th>
<th>Bendamustine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair Loss</td>
<td>Low blood counts (can be persistent)</td>
</tr>
<tr>
<td>Low blood counts</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>Rash</td>
</tr>
<tr>
<td>Rare – heart failure</td>
<td>Others</td>
</tr>
<tr>
<td>Prednisone side effects</td>
<td>Others</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
</tbody>
</table>

### What about non-chemotherapy treatment?

- **Relevance Study**
  
  **Study design**
  
  Patients with first-line FL (N = 1,000) → R (lenalidomide + rituximab) → CB, CRu, PR → R² maintenance (lenalidomide 1 yr + rituximab 2 yrs) → CR, CRu, PR → Rituximab maintenance (2 yrs)

- **No clear improvement over chemotherapy but may be similar in outcome**

  Fowler et al, ASCO 2018
Initial Therapy Summary

- Important to use a monoclonal antibody targeting CD20
- Combination partner can vary
- Important to consider side effects of treatment
- Most patients respond well to treatment and remain in remission

Maintenance Therapy

- Different ways to give maintenance
- Best data are for after R-CHOP
  - Role of maintenance after bendamustine is less clear
- Caution on side effects of prolonged treatment

- There is NO long-term survival benefit with maintenance therapy
- Goal is to prolong time before more treatment is needed

- Should be a discussion with your doctor and not a foregone conclusion
Follow-up after treatment for FL

- Time to first relapse is an important predictor of long term outcome

Considerations for relapsed FL

- Many of same considerations as at initial diagnosis
  - Patient fitness and other medical conditions
  - Overall goals of treatment and patient lifestyle
  - Disease burden (big vs small nodes)
  - Symptoms

- Time to relapse often influences treatment decisions

- Most patients will relapse several times over the course of the disease

- Consider clinical trial
Marginal Zone Lymphoma

- Several types of marginal zone lymphoma
  - Splenic MZL
  - MALT lymphoma (extranodal)
  - Nodal MZL

- MALT can be diagnosed in many parts of body

- Specific disease type influences treatment decision

MZL associated with infections

- Hepatitis C
- H. Pylori (stomach ulcers)
- C. Psittaci (ocular)
- Others – less common

- Patients with an infectious cause of MZL should receive treatment for the infection first….this can be curative.
Management Approach to MZL

- **Diagnosis**
- **Screen for Infections**
- **Infection Present?**
  - Yes → **Treat Infection**
  - No → **Evaluate Stage/Need for Treatment**
    - Isolated Lesion → **Radiation Therapy**
    - >1 Site or spleen only, asymptomatic → **Observe**
    - Recurrence or Progression to Symptomatic Disease → **Treatment**
      - Rituximab alone
      - R-Chemo

Treatment Considerations

- Similar treatments to follicular lymphoma
- Patients with isolated lesions can receive radiation therapy
- Most others who require treatment will benefit from a CD20 antibody +/- chemotherapy (frequently bendamustine)

- My approach: Frequently rituximab alone followed by bendamustine-rituximab if not a great response

- Maintenance less well established in marginal zone lymphoma
Chronic Lymphocytic Leukemia & Small Lymphocytic Lymphoma

• These are basically the same disease
  • Cells identical under the microscope
  • Prognosis is similar
  • Treatment is similar
  • Some patients have a WBC count that we follow, others have lymph nodes, some have both

• Prognosis is variable – important to complete appropriate work-up

CLL/SLL Prognostic Work-up (FISH)

Van Dyke et al, BJH 2016
Treatment of CLL/SLL is evolving

- Recent history:
  - Chemoimmunotherapy (FCR or BR)
  - Limited duration treatment
  - Long-term bone marrow toxicities
  - Some patients receiving FCR can have very long remissions
  - FCR likely better than BR in young patients – no difference in those > 65

- Two new studies compared chemo-immunotherapy to ibrutinib

Ibrutinib – Bruton’s tyrosine kinase inhibitor

- Oral, daily therapy
- Administered indefinitely
- Meant to disrupt important pathway in CLL/SLL
Chemo-immunotherapy vs ibrutinib

**YOUNGER PATIENTS**

Treatment-Naive CLL/SLL  
N=529  
- CLL (IWCLL criteria), or SLL (WHO criteria)  
- Disease requiring treatment  
- Age ≤70 years  
- No deletion of 17p13  
- ECOG PS 0-2

- Ibrutinib (QD) + Rituximab (7 cycles)
- Fludarabine + Cyclophosphamide + Rituximab (8 cycles)

**OLDER PATIENTS**

Treatment-Naive CLL  
N=523  
- CLL (IWCLL criteria)  
- CLL requiring treatment (IWCLL criteria)  
- Intermediate- or high-risk Rai stage

- Bendamustine + Rituximab (6 cycles)
- Ibrutinib (QD)
- Ibrutinib (QD) + Rituximab (6 cycles)

E1912 – FCR vs R-Ibrutinib in Young Pts

**PFS (All Randomized)**  
HR=0.352; 95% CI, 0.223-0.558; *P*<0.0001

**OS (All Randomized)**  
HR=0.168; 95% CI, 0.053-0.538; *P*=0.0003

Shanafelt et al, ASH 2018
Alliance Study – Older Patients

Considerations Front-line treatment CLL

- Chronic vs defined duration of treatment
- Finances
- Long-term mild toxicity vs short-term more significant toxicity
- What is long-term goal? Is time off of therapy meaningful?

<table>
<thead>
<tr>
<th>Ibrutinib</th>
<th>Chemo-immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic, indefinite treatment</td>
<td>6 months of treatment</td>
</tr>
<tr>
<td>Expensive</td>
<td>Low blood counts</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Bone marrow toxicity</td>
</tr>
<tr>
<td>Bleeding/bruising</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Infection risk</td>
<td></td>
</tr>
<tr>
<td>Arthralgias</td>
<td></td>
</tr>
</tbody>
</table>
New/Emerging Treatments

- Oral targeted therapies
  - Pi3 Kinase inhibitors
  - BTK Inhibitors
  - Venetoclax
  - Others (syk, Pikfyve, mTOR) inhibitors

- Immunotherapies
  - Vaccine
  - CAR-T
  - Monoclonal antibodies
    - Bispecific antibodies

- Combination approaches

Incorporation of Novel Therapies in iNHL

- FDA approvals:
  - Idelalisib, Duvelisib, Copanlisib
  - Ibrutinib
  - Venetoclax

- Most approvals are for monotherapies – combinations may be better
- Caution – some combinations are toxic

- Ongoing clinical trials are critical. Patients with relapsed indolent NHL are often ideal candidates due to slow progression of disease.
**Chimeric Antigen Receptor (CAR-T)**

CAR-T currently approved for aggressive NHL

- Used for patients with aggressive or transformed NHL
- Cellular therapies ARE available for other lymphoma types on study
- These therapies typically not considered for untreated patients
- Ask your physician about any potential trials for relapsed patients
**General Considerations**

- Many patients with indolent NHL can live "normal" lives
  - Full time work
  - Families
  - Travel
  - Hobbies
- But…..living with cancer is often a source of stress and anxiety
- Patients need ongoing support

**How to Help Loved Ones with Lymphoma**

- Provide support at level desired by patient
- Patient experience fluctuates over the course of the disease
  - Level of day-to-day support may wax and wane depending on disease status, symptoms, side effects, etc.
- Be an advocate for the patient but not their doctor
- Respect their wishes and decisions
- Take notes, ask questions, be another pair of eyes/ears
- If you use the internet, use reputable sources for information:
  - www.LLS.org
  - www.Lymphoma.org
Summary

• Indolent NHL is a variety of diseases with different treatments
• Many patients are observed (for years) before first therapy initiated
• Patients will be treated on several occasions over their disease course
• Newer therapies are approved/in development, including combinations
• Clinical trial enrollment critical to success of future treatments
• Ask questions and be informed!

Thank You!

Q&A SESSION
Treatment Advances for Slow-Growing Non-Hodgkin Lymphomas

• Ask a question by phone:
  – Press star (*) then the number 1 on your keypad.

• Ask a question by web:
  – Click “Ask a question”
  – Type your question
  – Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.
LLS EDUCATION & SUPPORT RESOURCES

• Information Specialists
  Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  – EMAIL: infocenter@LLS.org
  – TOLL-FREE PHONE: 1-800-955-4572

• Free Education Booklets:
  – www.LLS.org/booklets

• Free Telephone/Web Programs:
  – www.LLS.org/programs

• Live, weekly Online Chats:
  – www.LLS.org/chat

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• LLS Podcast, The Bloodline with LLS
  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.thebloodline.org

• Education Videos
  Free education videos about survivorship, treatment, disease updates and other topics: www.LLS.org/educationvideos

• Patti Robinson Kaufmann First Connection Program
  Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection

• Free Nutrition Consults
  Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition

• What to Ask
  Questions to ask your treatment team: www.LLS.org/whattoask

• Other Support Resources
  LLS Community, discussion boards, blogs, support groups, financial assistance and more: www.LLS.org/support
THANK YOU

We have one goal: A world without blood cancers