The Changing Face of Chronic Lymphocytic Leukemia

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Conflict of Interest

• none
Objectives

- Review the epidemiology of CLL
- Recognize the need for referral to CLL Clinics and the roles of the CCPN
- Define translational research and review its impact in patient care
Introduction

• CLL/SLL most prevalent lymphoid malignancy in North America

• Most advances in clinical care in the last decade
Clinical Epidemiology

• Incidence 7.5/100,000 per year in Manitoba

• Median Age 71.5

• Gender 1:3 in favor of males
Definitions- International Workshop on Chronic Lymphocytic Leukemia (iwCLL)

- **CLL**
  - monoclonal B lymphocytes, CD19+, CD5+ and CD23+ and weakly express surface immunoglobulin, CD20, CD79b and FMC7
  - require a peripheral blood B lymphocyte count of >5 x 10⁹/L

- **MBL- monoclonal B-cell Lymphocytosis**
  - require a peripheral blood B lymphocyte count of < 5 x 10⁹/L
To Be or Not to Be?
MBL

• Clinical MBL (ALC >3.2) rate of progression of 1-2% year

• Patients are followed yearly

• Advised in preventative options
# Negative Prognosticators in CLL

<table>
<thead>
<tr>
<th>Prognostic Marker</th>
<th>Better Prognosis</th>
<th>Worse Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;70 yrs</td>
<td>&gt;79 yrs</td>
</tr>
<tr>
<td><strong>Plasma vitamin D level</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Rai Stage</td>
<td>0, I and II</td>
<td>III and IV</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>&lt;12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Lymphocyte doubling time</td>
<td>&lt;12 months</td>
<td>&gt;12 months</td>
</tr>
<tr>
<td>Number of &quot;Smudge cells&quot;</td>
<td>&gt;30%</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>β2-microglobulin level</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Flow Cytometry B cell count</td>
<td>&lt;11 x 10⁹/L</td>
<td>≥11 x 10⁹/L</td>
</tr>
<tr>
<td><strong>CD38</strong></td>
<td>&lt;20% cells positive</td>
<td>≥20% cells positive</td>
</tr>
<tr>
<td><strong>ZAP-70</strong></td>
<td>&lt;20% cells positive</td>
<td>≥20% cells positive</td>
</tr>
<tr>
<td>FISH</td>
<td>Deletion 11q22-23, 17p13</td>
<td>Deletion 11q22-23, 17p13</td>
</tr>
<tr>
<td>IgVh gene</td>
<td>Mutated</td>
<td>Unmutated</td>
</tr>
</tbody>
</table>
Example 1

- 65 year old male
- WBC 12
- Absolute Lymphocyte count 4.0
Example 2

- 45 year old male Rai Stage 4
- Bulky adenopathy
- Early relapse post FCR
- 2nd CR post almemtuzumab awaiting allo transplant
Example 3

• 91 year old male

• Rai stage 0

• WBC 150

• Absolute lymphocyte count 145

• asymptomatic
WHY HAVE A DEDICATED CLL CLINIC?
Hematologist/Oncologist Disease-Specific Expertise and Survival: Lessons from Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

Tait D. Shanafelt, MD; Neil E. Kay, MD; Kari G. Rabe, MS; David J. Inwards, MD; Clive S. Zent, MD; Jose F. Leis, MD; Susan M. Schwager, Carrie A. Thompson, MD; Deborah A. Bowen, FNP; Thomas E. Witzig, MD; Susan L. Slager, PhD; and Timothy G. Call, MD
Improved Survival
Time to First Treatment
Treating CLL in 2012

Treatment Algorithm for CLL

- Alemtuzumab Containing Treatment
  - <65
    - BMT
    - PCR
    - Alemtuzumab
  - >65
    - Monitor
    - Alemtuzumab

- FCR
  - <2 year
    - A
  - >2 year FCR

- FR
  - <1 year
    - A
  - >1 year FR

- CLB/CYCLO
  - RCD

- Relapse

A: Ofatumumab, Solumedrol/Ritux, Bendamustine, Lenalidomide
No Survival Advantage
Summary

• Patients followed by CLL Hematologists or closely in contact had a longer time to first treatment
• Minimizing exposure to
  – Treatment related complications
  – Infections
  – Second malignancies
  – Myelodysplasia
• Early detection of Disease related complications
  – ITP, AIHA, hypogammaglobulinemia
• Improved survival
Where Does the CCPN Fit in?

• We function as team

• We require your help in closely following patients in a geographically challenging environment
• This includes:
  – Physical exams-adenopathy, splenomegaly
  – Monitoring CBC
  – Change in symptoms
  – Provide vaccinations
Therapeutic options

Treatment Algorithm for CLL

Alemtuzumab Containing Treatment

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BMT

>65
Monitor

PCR

Alemtuzumab

<2 year FCR

<65
Alemtuzumab

>65
BMT

A

>2 year FCR

A

<1 year FR

>1 year FR

CLB/CYCLO

RCD

FR

FR

Relapse

A: Ofatumumab
Solumedrol/Ritux
Bendamustine
Lenalidomide

A:

CancerCare Manitoba
Advantages of the Clinic

• CLINICAL TRIALS

• PARTICIPATION IN RESEARCH ACTIVITIES
The Changing Face of Chronic Lymphocytic Leukemia

The Cutting Edge of Research

Ms. Donna Hewitt RN
Translational Research Nurse
Conflict of Interest

• none
Clinical Trials

- Research study to find new methods for diagnosis, treatment, management or prevention
- Informed consent
- Structured to provide consistency
- Results in Evidence based care
- Often compares best practice to new protocol
Clinical Trials

**Advantages**

- Access to new drugs, testing, technology
- May benefit from new treatment
- Patients are carefully monitored requiring more clinic visits
- Actively helping self and future patients

**Disadvantages**

- Need to travel to get treatment
- Not all trial patients receive new treatment
- Treatment may not be as effective
- May produce unanticipated side effects
Translational Research

• Includes a team based approach
  – molecular origins of cancer cells
  – regulation of genetic programming
  – biochemical action of drugs

• Clinicians observe trends and ask important questions, which scientists in the laboratory or epidemiologists can investigate
"Translational research transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality."
Manitoba Blood and Marrow Bank

- Consented patient information
- Blood
- Bone marrow
- DNA from buccal swabs
- Urine
- Permission to contact for future research
- Blood samples from age matched controls
Translational Research

• We have 724 CLL patients enrolled including those with precursor state

• Blood samples are collected ongoing throughout patient journey

• Researchers must obtain Ethics approval
Projects Supported by Manitoba Blood and Marrow Bank

**Local projects:**
- Mutational analysis
- Epidemiology of chronic lymphocytic leukemia and SLL in Manitoba
- Relevance of Telomeres in CLL
- Gefitinib as a novel therapy in ZAP-70 positive CLL
- HDAC Inhibitor Valproic Acid as an effective treatment for CLL
- Role of the microenvironment in CLL migration and adhesion.
- Epigenetic dysfunction in CLL
- Metabolic Deregulation in Leukemia
- Valproic Acid (VPA) as a Chemotherapy for CLL

**External Projects**
- McGill University Montreal
- Cross Cancer Institute, Edmonton
- Saskatoon Cancer Centre
- University of Texas
- University of Oxford, England
Gene3c Study of CLL Families

Goal is to understand role of genetics and interrelation with environment.

- Study uses samples from high risk families, both affected and non affected members. Participants fill out environmental questionnaires.
Genetic Study of CLL Families

- Index patient consented, blood drawn
- They do family history
- Pedigree is drawn
- Index patient asks family if research nurse can speak to them
- Information sent, consented, blood drawn in own community, questionnaires
- They choose if want results, counseling
CLL Clinic

• Aims to provide the best care

• Active participation in research

• Active and open communication between the CCPN and the CLL clinic
Which of the statements are TRUE?

• MBL patients should be referred to the CLL Clinic

• CLL patients are treated with a wide variety of treatment modalities

• Participation in research activities is optional

• All of the above