Classification Diagnostic Tools and Treatment of Non-Hodgkin Lymphoma

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Douglas E. Gladstone, MD
Clinical Director IPOP
Associate Professor of Oncology
Sidney Kimmel Comprehensive Cancer Center
at Johns Hopkins
Disclosures

• None
Leukemia and Lymphoma

• Cancer of white blood cells
  – Lymphoma
    • When they get caught up in the lymph nodes
  – Leukemia
    • When they freely circulate in the blood stream
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolent</td>
<td>Aggressive</td>
<td></td>
</tr>
<tr>
<td>Relatively long survival</td>
<td>Short survival without therapy</td>
<td></td>
</tr>
<tr>
<td>Nondestructive growth</td>
<td>Destructive growth</td>
<td></td>
</tr>
<tr>
<td>No cellular atypia</td>
<td>Cellular atypia</td>
<td></td>
</tr>
<tr>
<td>Respect privileged sites</td>
<td>Invade privileged sites</td>
<td></td>
</tr>
<tr>
<td>Regulatory influences</td>
<td>Autonomous</td>
<td></td>
</tr>
<tr>
<td>Fail to grow in culture</td>
<td>Immortalized in culture</td>
<td></td>
</tr>
</tbody>
</table>
Goal of this Talk

• To request a new NHL classification system based on cancer biology

• Three malignant conditions:
  • Diffuse large B cell
  • Mantle Cell
  • Chronic Lymphocytic Leukemia
Diffuse Large B cell lymphoma

Is there an important clinical subdivision?
Diffuse Large B cell Lymphoma

- Classification based on histology and IHC
  - Germinal center (GCB)
  - Activated B-cell (ABC)
GC DLBCL & ABC DLBCL by IHC

Hans et al, Blood 2004
GC vs ABC

Clinical Outcomes

Alizedah AA et al, Nature 2000
Rituximab & GC vs ABC
rituximab improves survival of both subtypes

Fu, K et al 2008, JCO
GC vs ABC subset
CORAL Trial of RICE v DHAP

- Which salvage regimen is the best?

CD20+ DLBCL
Relapsed/Refractory

R-ICE x 3
R-DHAP x 3

SD/POD → Off
PR/CR →

RANDOMIZE

ABSECT

RANDOMIZE

R x 6

Obs

N=249

- Place of immunotherapy post transplantation?
Coral: COllaborative trial in Relapsed Aggressive Lymphoma

GC vs ABC

- Patients treated with GC DLBCL have an marginally improved outcome when treated with R-DHAP  Thieblemont et al 2011 JCO

Gisselbrecht et al, 2010 JCO
Low Grade Lymphomas

Are there an important clinical subdivisions?
Mantle Cell Lymphoma

Just another low grade lymphoma?

- Diagnosis
  - Flow Cytometry: CD5+, CD20+, CD23-
  - Genetics
    - cyclin D1 positive
    - BCL-1 positive
    - T(11,14)
- Relatively short survival (high grade paradigm)
- Incurable with chemotherapy (low grade paradigm)
Immunoglobulin Heavy Chain Variable Region Mutational Status

• Somatic hypermutation (SHM) of Ig
  • Diversification: turning a naïve B cell to a high-affinity antibody producer
• SHM is thought to occur in the germinal center after antigen stimulation
  • often dependent on T cells
Mantle Cell Lymphoma

Immunoglobulin Heavy Chain Variable Region Mutational Status

• IGHV mutational status in MCL is often **UNMUTATED**
• This may explain the variable clinical outcomes in these patients

Agathangelidis et al, 2011 Sem Cancer Bio
Chronic Lymphocytic Leukemia

• Stage Rai
  0: lymphocytosis (L)
  I: (L) + nodes
  II: (L) + spleen or liver
  III: (L) + anemia
  IV: (L) + low PLT

• Flow Cytometry
  – CD 5+, CD20+, CD 23+
Chronic Lymphocytic Leukemia

Prognosis: Background

- Clinical correlates
  - Stage
  - WBC doubling time
  - Marrow histology
Chronic Lymphocytic Leukemia

Prognosis: Background

- Interphase FISH
- Immunoglobulin variable region heavy chain (IGHV) mutational status
- CD38
- ZAP 70
IGHV Mutational Status is Prognostic in del(13q) CLL

Hopkins Experience

- Studied 79 patients
  - 196 cases of CLL (2004-2010)
    - 79 (40%) had FISH and IGHV
- Follow-up 4.5 (range: 0-22) years

Gladstone et al, 2011 Leuk Lymphoma
IGHV Mutational Status is Prognostic in del(13q) CLL

Hopkins Experience

- **Unmutated** IGHV sequences occur 50% of the time
- The majority of patients with del (13q) only disease will have a **mutated** sequence

Gladstone et al, 2011 Leuk Lymphoma
IGHV Mutational Status is Prognostic in del(13q) CLL

Progression to Advanced Disease

Gladstone et al, 2011 Leuk Lymphoma
IGHV Mutational Status is Prognostic in del(13q) CLL

Likelihood of Receiving Treatment

Gladstone et al, 2011 Leuk Lymphoma
IGHV Mutational Status is Prognostic in del(13q) CLL

Overall Survival

Gladstone et al, 2011 Leuk Lymphoma
IGHV Mutational Status is Prognostic in del(17p)/del (11q) CLL

Hopkins Experience

• Studied 66 patients
  • Screened 159 cases of CLL with a resultant IGHV sequence (2006-2011)
    • 66 (41%) del(11q)/del(17p)
  • Follow-up 3.1 (range: 0.1-19.4) years

Unpublished data
In high-risk cytogenetic groups, an unmutated IGHV sequence is much more frequent.

Hopkins Experience

- 66 high risk patients
  - 50 (76%) Unmutated
  - 16 (24%) Mutated

Unpublished data
IGHV Mutational Status is Prognostic in del(17p)/del (11q) CLL

Unpublished Data
IGVH Mutational Status and the CLL Cancer Stem

CLL with chromosomal aberrations and known IGVH mutational status

Patient #1
Mutated -13q

Patient #2
Unmutated -13q-11q+12

Unmutated CLL: very small 34+19_{pos/dim} population

Mutated CLL: not present

This population contains the abnormal karyotype reported in the bulk CLL cells.

M. Showel, MD: unpublished data
Where we are
Leukemia and Lymphoma

• Cancer of white blood cells
  – Lymphoma
    • When they get caught up in the lymph nodes
  – Leukemia
    • When they freely circulate in the blood stream
Where I Hope We Go
Classification Based on the Origin of the Cancer Stem Cell

- Pre-Germinal
  - Unmutated CLL
  - Unmutated MCL

- Germinal
  - Mutated CLL
  - Mutated MCL
  - GC DLBCL

- Post Germinal
  - Pre B cell ALL
  - Burkitts

- unnamed
  - DLBCL
  - Multiple Myeloma