GRADING FOLLICULAR LYMPHOMA: THE BIG GUYS AND THE SMALL GUYS

Solomon Graf, MD
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Outline

- Case
- Review of FL pathology, prognosis
- Grading of FL
  - Grade 3 disease
  - High proliferative index in grade 1/2 disease
  - “Pediatric FL”
- Future of FL classification
Clinical case

- 57 yo man transfers care to VA
- 1st presented 2007 with adenopathy, splenomegaly
  - Pathology: low grade non-hodgkin’s lymphoma
- Received 6 cycles of R-CHOP then R for 2 years
- Now without evidence of disease
- Inquires about prognosis
Normal: Naïve B cell leaves marrow, enters secondary lymphoid tissue, and undergoes controlled apoptosis in the germinal center if no antigen

FL: t14;18 causes Bcl-2 overexpression that inhibits apoptosis and circumvents requirement of ongoing antigen stimulation

Note: t14;18 is neither necessary nor sufficient for diagnosis; instead considered a “first hit”
High power: Admixture of centrocytes (small, cleaved) and centroblasts (large, noncleaved): the germinal center B cells

Low power: Maintains at least partially follicular pattern.
“An indolent, incurable disease”
Generally responsive to chemotherapy with eventual relapse – repeated
Transformation to DLBCL and resistance to treatment portend poor outcomes
Large study from Nebraska (2006) established in multivariate analysis three independent predictors of survival:
- Sex: HR of death being a woman 0.6
- FLIPI score
- Grade of disease

Ganti A K et al. Ann Oncol 2006;17:920-927
1 Point each for:
- Age greater than 60 years
- Ann Arbor Stage III or IV disease
- Greater than 4 lymph node groups involved
- Serum hemoglobin less than 12 g/dL
- Elevated serum LDH

1980s: many grading schema developed to account for relative numbers of centroblasts affecting outcome in FL

Berard scoring (modified): best stratification for both OS and PFS
- FL grades 1, 2, and 3 according to centroblast # per HPF (0-5, 6-15, > 15)
- Centroblasts/HPF in 10 neoplastic follicles

Limitations
- Reproducibility
- Grade 3 clearly morphologically heterogeneous

WHO 2008 established FL 1-2 of 3, 3A (centrocytes present) and 3B (sheets of centroblasts)
Distinguishing 3A from 3B is technically challenging and they do not clearly have divergent outcomes (these after upfront treatment with anthracycline-containing regimens)

Outcomes in FL3 reported by different groups have had highly variable results: Median survival 2 – 20 yr

Grade 3 = 30% of FL

Comparison of the outcomes of patients with FL3 in reported clinical series

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Median age (years)</th>
<th>Median survival (months)</th>
<th>FFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al. 1973 [25]</td>
<td>29</td>
<td>53</td>
<td>45</td>
<td>NR</td>
<td>35% (4.5 years)</td>
</tr>
<tr>
<td>Osborne et al. 1980 [12]</td>
<td>16</td>
<td>51</td>
<td>31</td>
<td>NR</td>
<td>50% (5 years)</td>
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<tr>
<td>Glick et al. 1982 [11]</td>
<td>25</td>
<td>56</td>
<td>47</td>
<td>NR</td>
<td>50% (4 years)</td>
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<tr>
<td>NCI 1982 [26]</td>
<td>44</td>
<td>55</td>
<td>36</td>
<td>NR</td>
<td>40% (5 years)</td>
</tr>
<tr>
<td>Stewart et al. 1986 [27]</td>
<td>53</td>
<td>54</td>
<td>25</td>
<td>NR</td>
<td>60% (6.25 years)*</td>
</tr>
<tr>
<td>Horning et al. 1987 [28]</td>
<td>50</td>
<td>NR</td>
<td>132</td>
<td>NR, Not reached</td>
<td>22% (10 years)</td>
</tr>
<tr>
<td>Anderson et al. 1993 [8]</td>
<td>107</td>
<td>63</td>
<td></td>
<td></td>
<td>46% (3 years)</td>
</tr>
<tr>
<td>Bartlett et al. 1994 [10]</td>
<td>96</td>
<td>52</td>
<td></td>
<td></td>
<td>42% (10 years)</td>
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<tr>
<td>Wendum et al. 1997 [13]</td>
<td>89</td>
<td>54</td>
<td>73</td>
<td>NR</td>
<td>40% (5 years)</td>
</tr>
<tr>
<td>Rodriguez et al. 1999 [9]</td>
<td>100</td>
<td>59</td>
<td>141</td>
<td>39% (5 years)</td>
<td></td>
</tr>
<tr>
<td>Rodriguez et al. 2000 [7]</td>
<td>62</td>
<td>57</td>
<td>61</td>
<td>37% (10 years)</td>
<td></td>
</tr>
<tr>
<td>Chau et al. 2003 [29]</td>
<td>55</td>
<td>53</td>
<td>266</td>
<td>31% (10 years)</td>
<td></td>
</tr>
<tr>
<td>Current study</td>
<td>177</td>
<td>60</td>
<td>113</td>
<td>31% (10 years EFS)</td>
<td>45% (10 years)</td>
</tr>
</tbody>
</table>

Ganti A K et al. Ann Oncol 2006;17:920-927
The grade (3) debate

- FL1/2 are genetically and immunophenotypically homogenous [90% express BCL2, CD10, and BCL6]
- FL3 are heterogeneous, with FL3B, in particular, sometimes similar to FL1/2 and other times to DLBCL

<table>
<thead>
<tr>
<th></th>
<th>CD10+ MUM1/IRF4-</th>
<th>CD10- MUM1/IRF4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL1/2</td>
<td>25/25</td>
<td>0/25</td>
</tr>
<tr>
<td>FL3A</td>
<td>4/5</td>
<td>0/5</td>
</tr>
<tr>
<td>FL3B</td>
<td>8/19</td>
<td>8/19</td>
</tr>
<tr>
<td>DLBCL/FL3B</td>
<td>2/16</td>
<td>7/16</td>
</tr>
</tbody>
</table>

CD10 (and BCL6) = germinal center B cells
IRF4 (and BCL2) = activated B cells

Horn H et al. Haematologica 2011;96:1327-1334
Grade 3 is biologically heterogeneous.

Separating grade 3 into 3A and 3B is standard, but is problematic and also not very predictive.

Grade 3 has a heterogeneous set of outcomes:
- Survival curves in some analyses appear to plateau, in contrast to grade 1/2.
Back to the case

- FLIPI intermediate

- Original LN biopsy reviewed
  - “Lymphoid follicles with small centrocytes admixed with large centroblasts (< 15/HPF)”
  - Immunophenotype: CD20+, CD10+, BCL-2 overexpressed
  - Low grade (1-2) follicular lymphoma with hi proliferative index

Courtesy of Dr. Dong
1. High PI found in 18% of low grade FL
2. LG-HPI cases behaved more like FL G3 than LG-LPI

Cutoff LG-LPI vs LG-HPI = 30% Ki67 positive cells

American Journal of Surgical Pathology.
“Pediatric FL” – HPI and no BCL2 rearrangement

- FL in children: normal to achieve sustained CR
- Cohort of 27 “PFL” (<40 yrs old)
  - 21 were stage I cases and lacked BCL2 rearrangement (FISH correlated with IHC) and had high Ki67 (> 30%)
  - 6 were stage III/IV and had either/both BCL2 rearrangement and low Ki67
- The BCL2-N/HPI group had uniformly good outcomes
- No histologic grade preference
  - 10/27 grade 3

Louissaint A et al. Blood 2012;120:2395-2404
High proliferative index can cause grade 1/2 FL to behave like grade 3 FL — if BCL2 rearrangement is present.

High proliferative index in setting of no BCL2 rearrangement (in stage I disease) results in the pediatric FL phenotype.

How to improve classification of FL beyond FLIPI and WHO 2008?
Lymphoma/Leukemia Molecular Profiling Project (NIH)

Two “gene expression signatures” with statistically robust predictive power emerged from microarray profiling

These, when divided by quartile, effectively stratified survival

The expressed genes, surprisingly, were associated with immune response pathways in the non-neoplastic cells of the tumor

NEJM. 2004 Nov 18;351(21):2159-69
FL B cells are impossible to grow in vitro without stromal cells and cytokines.

The FL tumor is characterized by the maintenance of the follicular structure.

Microenvironment thought to:
- Support tumor growth and survival
- Suppress antitumoral immune response

Case: 57 yo man with LG-HPI FL thus far has had a CR nearly 4 yrs out of therapy, consistent with survival plateau of LG-HPI / FLG3

Histologic grading of FL is important to clinical outcomes, but incomplete

Tumor microenvironment affects disease outcomes and will ultimately be included in disease classification
Thanks

- Dr. Chauncey – Topic suggestion and review
- Dr. Ulrickson – Literature orientation
- Dr. Dong – Material and discussion