Low Grade Lymphomas: Where Do the New Therapies Fit In?

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Areas to be covered...

- Prognostic scoring – FLIPI
- Approach to early stage disease
- Management of advanced stage disease
- Consolidation – RIT
- Maintenance therapy
- Relapsed / refractory disease
- Novel agents
## FLIPI vs FLIPI-2

<table>
<thead>
<tr>
<th>Feature</th>
<th>FLIPI vs FLIPI-2</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>( \leq 60 ) yrs vs ( &gt; 60 ) yrs</td>
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<tr>
<td>Serum LDH</td>
<td>Normal vs elevated</td>
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<tr>
<td>Ann Arbor disease stage</td>
<td>I, II vs III, IV</td>
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<tr>
<td>Hemoglobin</td>
<td>( \geq 12 ) g/dl vs ( &lt; 12 ) g/dl</td>
</tr>
<tr>
<td>Number of nodal areas</td>
<td>( \leq 4 ) vs ( &gt; 4 )</td>
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</tbody>
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- Risk: low (0, 1), intermediate (2), high (3-5)
- Predictive of TTF, risk of death (hazard ratio)
- Retrospective (1985-1992)

(Blood 2004; 104:1258-1265)
FLIPI vs FLIPI-2

• Prospective (2003-2005) – rituximab era
• PFS (surrogate endpoint for OS)

Age
≤60 yrs vs > 60 yrs

β-2 microglobulin
Normal vs elevated

Marrow involvement
+ vs -

Hemoglobin
>12 g/dl vs < 12 g/dl

Longest diameter, lgest LN
≤6 vs >6

• Three risk groups

( J Clin Oncol 2009; 27:4555-4562)
Management of Early Stage Disease

• 10% stage I, IIA
• Standard of care: involved field radiation therapy, with curative intent
• Dose:
  – 24-30 Gy for nonbulky disease with rapid response
  – 36 Gy for bulky or slowly regressive disease
• Improved DFS/OS than other approaches (obs)
• CR or PR – follow-up q 3-6 months X 5 yrs, then yearly
Single Agent Rituximab

- Improved patient outcomes c/w pre-rituximab era
- Rituximab induction, followed by rituximab maintenance
- Response rates – 72-73% (CR 31-36%)
- Median TTP – 2.2 yrs
- Patient selection
  - Low risk disease
  - Unable to tolerate more aggressive therapy

Rituximab-Chemotherapy Combinations

- Improved ORR, remission duration, PFS, OS (some)
- NCCN recommended regimens
  - Rituximab-bendamustine (category 1)
  - R-CHOP (category 1)
  - R-CVP (category 1)
  - Rituximab-fludarabine (category 2A)
  - R-FND (category 2A)

- Grade 3 follicular NHL – treat as DLBCL
Rituximab-Chemotherapy Combinations

• R-CHOP most frequently used (LymphoCare study)
  – Median TTP: 82 months
  – Median remission duration: 84 months

• German study – CHOP vs R-CHOP
  – Relative risk for treatment failure reduced by 60%
  – Significant OS advantage (2-yr OS 95% vs 90%, p=0.016)

(J Clin Oncol 2004; 22:4711-4716)
Rituximab-Chemotherapy Combinations

• German study – R-bendamustine vs R-CHOP
  – Indolent, mantle cell NHL
  – BR resulted in significantly prolonged PFS c/w R-CHOP (55 vs 33 months, p=0.00012)
    • Follicular NHL patients (p=0.028)
  – Median time to next treatment (NR vs 38 months, p=0.001)
  – Improved toxicity profile – less:
    • Neutropenia (11% vs 47%, p<0.0001)
    • Leukopenia (12% vs 38%, p<0.001)

(ASH 2009; Abstract 405)
RIT Consolidation Therapy

- CVP – RIT
  - Median F/U 8.4 yrs, median remission duration NYR (3-111+ months)
  - 5-yr OS / PFS – 83% / 56%

- Fludarabine X 3 – RIT
  - 10-yr OS / PFS – 51% / 69%
RIT Consolidation Therapy

• Phase II SWOG trial
  – CHOP X 6, Bexxar 1-2 months later
  – ORR 91% (CR 69%)
  – 5-yr OS 87%; 5-yr PFS 67%
  – Both 23% better than prior SWOG trials w/CHOP
  – Conclusions – early disease progression, deaths, declining PS during CHOP limit number of patients who can benefit from consolidation approach

(ASH 2010; Abstract 591)
Maintenance Therapy Following Induction Therapy

• Rituximab maintenance
  – After R weekly X 4, R q 2 mos X 2 yrs, vs Obs
  – Median F/U 9.5 yrs, median EFS 24 vs 13 months, p <0.001)

• PRIMA study
  – Frontline R-CHOP, R-CVP, or R-FCM, then randomization to R q 2 mos X 2 yrs vs Obs
  – Median F/U 3 yrs –
    • Median PFS (75% vs 58%, p < 0.001)
    • Median OS – no significant difference

(J Clin Oncol 2010; 28: 4480-4484; Lancet 2011; 377: 42-51)
Issues with Maintenance Rituximab

• Hypogammaglobulinemia – sometimes lengthy
• Significant increase in grade 3/4 infections
  – 9.7%, c/w 2.4% with observation – EORTC
  – 24% c/w 17% - PRIMA study
• Higher rates of neutropenia
• Schedule – how often, how long?
• Effect of maintenance rituximab on subsequent therapy
Relapsed / Refractory Disease

• Issue of transformation
• Observation
• Similar therapy as used frontline
• RIT
• Bendamustine, alone or with rituximab
  – B – ORR 75% (17% CR); median remission duration 9.2 mos; median PFS 9.3 mos
  – BR – ORR 90% (60% CR); median PFS 2 yrs
  – BBR – ORR 86% (53% CR)

Novel Agents in Development

• Lenalidomide
  – ORR 23-42%

• Lenalidomide + rituximab
  – ORR 88% (55% CR)
    (ASH 2009; Abstract 1679)
  – CALGB 50401
  – Lenalidomide issues – incidence of second primary malignancies
    (ASCO 2011; Abstracts 8007, 8008)

• Bortezomib + rituximab
  (ASH 2010, Abstract 857)
Novel Agents in Development

- Ofatumumab
  - ORR 20-63%
  - Median TTP – 32.6 months
- GA-101 – 3rd generation glyco-engineered type II MoAb
- Epratuzumab + rituximab – CALGB 50701
  - ORR 84% (335 CR)

(Blood 2008; 111: 5486-5495; ASH 2010, Abstracts 1585, 427)
Novel Agents in Development

- CMC-544 (inotuzumab ozogamicin) – CD22 MoAb
  - ORR 66-85%
- SAR 3419 – radioimmunoconjugate
- CAL-101 – phosphatidylinositol 3-kinase (PI3K)-inhibitor
- PCI-32765 – inhibitor of B-cell receptor signaling molecule

(J Clin Oncol 2010; 28: 2085-2093; ASH 2010; Abstracts 430, 964, 1777; ASH 2009, Abstract 585)
Conclusions

• We have come a great distance, but still have a long way to go

• There will not be many “home runs” like rituximab

• The intercalation of new agents into old therapeutic paradigms will likely lead to treatment advances in follicular NHL
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