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• John P. Leonard, MD: Advisor/Consultant: Abbott, Biotest, Calistoga Pharmaceuticals/Gilead, Celgene, Cell Therapeutics, Cephalon, GlaxoSmithKline, Hospira, Immunomedics, Johnson & Johnson, MedImmune, Millennium Pharmaceuticals, Morphosys, Sanofi Aventis, Seattle Genetics

• Julie Vose, MD, MBA: Research Grant: Allos Therapeutics, Bristol-Myers Squibb, Celgene, Genentech, GlaxoSmithKline, Incyte Corp., Millennium Pharmaceuticals, Onyx Pharmaceuticals, Pharmacyclics, S*Bionet, US Biotest

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Non-faculty content contributors and/or reviewers reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

Latha Shivakumar, PhD; Bradley Pine; Blair St. Amand; Jay Katz; Paul M. Barr, MD: Nothing to Disclose

Educational Objectives

At the conclusion of this activity, participants should be able to demonstrate the ability to:

• Review the current approaches for the treatment of relapsed/refractory NHL

• Compare the various available treatments and choose the optimal treatment based on patient characteristics and recently presented data from ongoing clinical studies in relapsed/refractory NHL

• Identify key investigational agents from ongoing clinical studies in relapsed/refractory NHL
Oncology Exchange
Emerging Strategies in Relapsed/Refractory Non-Hodgkin’s Lymphoma

Paper Audience Response Questions

• During the course of the program Audience Response Questions will be asked to determine the current knowledge of the audience
• These questions will not be graded and are for outcomes purposes only
• Please record your answers on your evaluation form located in your packet

Non-Hodgkin Lymphoma (NHL)

• Most common hematological cancer
• Seventh-most common cancer in United States
• Approximately 65,000 cases of NHL diagnosed in 2010
• More than 20,000 deaths from NHL reported in 2010
• As of 2007, approximately 430,000 people were living with a history of NHL in the United States


Frequency of NHL Subtypes In Adults

- Follicular lymphoma (22%)
- Marginal zone B-cell lymphoma nodal type (1%)
- Lymphoplasmacytic lymphoma (1%)
- MALT = mucosa-associated lymphoid tissue.
- Marginal zone B-cell lymphoma MALT type (5%)
- Small lymphocytic lymphoma (3%)
- Diffuse large B-cell lymphoma (31%)
- Composite lymphomas (13%)
- Peripheral T-cell (8%)
- Marginal zone B-cell lymphoma (6%)
- Other subtypes with a frequency <2% (9%)
- Small lymphocytic lymphoma (4%)
- Diffuse large B-cell lymphoma (6%)
- MALT lymphoma (22%)
- Follicular lymphoma
Two Major Lymphoma Clinical Paradigms

- Aggressive histologies—diffuse large B cell
  - Practical objective of treatment: cure
  - Reasonably good clinical prognostic tools
  - Most patients treated the same (R-CHOP)
  - Unmet need: one-third not cured; reduce toxicity of treatment
- Indolent histologies
  - Practical objective of treatment: long disease control
  - Fair clinical prognostic tools
  - Treatment choice balances efficacy and toxicity
  - Unmet need: cures, rational treatment selection

R-CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone, with rituximab.

Emerging Prognostic Tools for FL

- Clinical
  - IPI, FLIPI, FLIPI-2
- Pathologic
- Molecular profiling
- Response-based
  - MRD, CR vs PR, PET
  - Duration of current/prior response
  - Interesting potential, but limited data to date, indicating that these should be used to guide therapy or drug development

FL = follicular lymphoma; IPI = International Prognostic Index; FLIPI = Follicular Lymphoma International Prognostic Index; FLIPI-2 = Follicular Lymphoma International Prognostic Index 2; MRD = minimal residual disease; CR = complete response; PR = partial response; PET = positron emission tomography.

Overall Survival In FL by FLIPI

Risk Group
Low: 0-1  Intermediate: 2  High: 3-5

<table>
<thead>
<tr>
<th>No. of Factors</th>
<th>% of Patients</th>
<th>5-y OS (%)</th>
<th>10-y OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>36</td>
<td>90.6</td>
<td>70.7</td>
</tr>
<tr>
<td>Intermediate</td>
<td>37</td>
<td>77.8</td>
<td>50.9</td>
</tr>
<tr>
<td>High</td>
<td>27</td>
<td>52.5</td>
<td>35.5</td>
</tr>
</tbody>
</table>

LDH = lactate dehydrogenase; OS = overall survival.

Current Treatment Options in Indolent Lymphoma

- Observation
- Single-agent rituximab ± maintenance
  - Can adding other biologics enhance activity without major toxicity?
- Chemotherapy + rituximab ± maintenance
  - What is the best chemotherapy?
  - What is the role of maintenance rituximab?
- RIT
  - Alone or as consolidation
- SCT options in first (second, later) remission
- Novel/investigational agents

RIT = radioimmunotherapy; SCT = stem cell transplantation.

Managing Patients With Relapsed and Refractory FL

Outcomes With Sequential Chemotherapy in FL—1995

- 212 patients, newly diagnosed FL over 20 years
- Treated generally with chlorambucil, CVP, CHOP

<table>
<thead>
<tr>
<th>Line</th>
<th>Median Response Duration (months)</th>
<th>Survival From Response (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>31</td>
<td>9.6</td>
</tr>
<tr>
<td>2nd</td>
<td>13</td>
<td>4.9</td>
</tr>
<tr>
<td>3rd</td>
<td>13</td>
<td>3.5</td>
</tr>
<tr>
<td>4th</td>
<td>8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

CVP = cyclophosphamide, vincristine, and prednisone.

Limitations of These Data

- Retreatment with same agents versus different approaches
- Pre-rituximab era
- New therapeutic options now available
- More rigorous monitoring/surveillance common now
  - For better or worse

Case 1

- A 60-year-old male presented with follicular, grade 2 NHL with symptomatic diffuse LAN in the 3- to 4-cm range; he is treated with R-CHOP × 6 cycles and then observed.
- 2.5 years later, he presents with axillary and abdominal LAN in the 3- to 4-cm range on routine imaging
- Blood chemistries, LDH, and complete blood counts are normal, and bone marrow biopsy shows no evidence of involvement with lymphoma

ARS Question 1

Please record your answer on your evaluation form now.

The preferred management for this patient is:

A. Close observation and monitoring
B. Single-agent rituximab × 4 doses
C. Single-agent rituximab + maintenance rituximab
D. Rituximab-fludarabine combination regimen
E. Bendamustine-based regimen
F. RIT
G. RICE or similar regimen
H. RICE or similar regimen, followed by ASCT

LAN = lymphadenopathy

RICE = rituximab, ifosfamide, carboplatin, etoposide; ASCT = autologous SCT
ARS Question 1

The preferred management for this patient is:

A. Close observation and monitoring
B. Single-agent rituximab × 4 doses
C. Single-agent rituximab + maintenance rituximab
D. Rituximab-fludarabine combination regimen
E. Bendamustine-based regimen
F. RIT
G. RICE or similar regimen
H. RICE or similar regimen, followed by ASCT

*All the answers are reasonable choices for this patient.*

RICE = rituximab, ifosfamide, carboplatin, etoposide; ASCT = autologous SCT.

Considerations in Choice of Therapy for Second-line Treatment

- Consider transformation
- Symptoms
- Bulk of disease
- Age and performance status
- Efficacy of last treatment
  - Response, time since, tolerability
  - Similar versus something different
- Patient preferences

Specific Considerations for This Patient

- Transformation clinically unlikely
- No symptoms
- Nonbulky disease
- Age and performance status
  - SCT option, perhaps
- Last treatment
  - Effective but would prefer more durability
**Treatment Options for This patient**

- Chemotherapy + rituximab
  - Bendamustine favored over fludarabine
- Single-agent rituximab
  - Asymptomatic, but unlikely to be durable
- RIT
  - Well tolerated, chance at durability
- Combination chemotherapy + SCT
  - Potentially durable, though toxicity


**Chemotherapy Data for Recurrent Indolent NHL (Until Recently)**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>RR</th>
<th>TTF/PFS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab mono</td>
<td>166</td>
<td>48%</td>
<td>13</td>
</tr>
<tr>
<td>FCM</td>
<td>30</td>
<td>70%</td>
<td>21</td>
</tr>
<tr>
<td>Rituximab + FCM</td>
<td>35</td>
<td>94%</td>
<td>Not reached (median follow-up: 3 y)</td>
</tr>
<tr>
<td>CHOP</td>
<td>231</td>
<td>72%</td>
<td>20</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>234</td>
<td>85%</td>
<td>33</td>
</tr>
</tbody>
</table>

FCM = fludarabine, cyclophosphamide, mitoxantrone; RR = relative risk; TTF = time to treatment failure; PFS = progression-free survival.


**Caveats From Data in This Population**

- Heterogeneous prior therapies
- Heterogeneous prior use of rituximab
- Heterogeneous prior use of R-CHOP and rituximab-bendamustine
- How much these data apply to an individual patient today is unclear
- Expect that, with better upfront therapy, a "resistant" patient will be "worse" with respect to prognosis
Phase II Trial of Bendamustine in Rituximab-refractory NHL: Results
Multicenter, nonrandomized, open-label, single-arm trial

<table>
<thead>
<tr>
<th>Patient Subset</th>
<th>N</th>
<th>ORR</th>
<th>CR/CRu</th>
<th>PR</th>
<th>DOR (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable patients</td>
<td>74</td>
<td>77%</td>
<td>34%</td>
<td>43%</td>
<td>6.67</td>
</tr>
<tr>
<td>Prior Therapies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with ≥2 prior therapies</td>
<td>40</td>
<td>75%</td>
<td>30%</td>
<td>45%</td>
<td>5.3</td>
</tr>
<tr>
<td>Prior ASCT</td>
<td>6</td>
<td>67%</td>
<td>17%</td>
<td>62%</td>
<td>2.6</td>
</tr>
<tr>
<td>Alkylator-refractory patients</td>
<td>23</td>
<td>61%</td>
<td>15%</td>
<td>48%</td>
<td>7.7</td>
</tr>
<tr>
<td>Rituximab-refractory patients</td>
<td>8</td>
<td>82%</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- CR = complete response
- CRu = unconfirmed complete response
- DOR = duration of response
- ORR = overall response rate

Histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>FL</th>
<th>SLL</th>
<th>MCL</th>
<th>Marginal Zone</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>59</td>
</tr>
</tbody>
</table>

- FL = follicular lymphoma
- SLL = small lymphocytic lymphoma
- MCL = mantle cell lymphoma
- LPL = lymphoplasmacytic lymphoma
- MZL = marginal zone lymphoma


Phase II Trial of Bendamustine in Rituximab-refractory NHL: PFS

PFS (All Treated Patients)

- Median duration of PFS: 39 months
- Median OS: 65 months

Safety:

- Grade 3
- Grade 4
- % of Grade 3/4

- Neutropenia: 11
- Thrombocytopenia: 0
- Anemia: 0


Bendamustine + Rituximab in Relapsed/Refractory Indolent and MCL: Efficacy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>FL (n = 24)</th>
<th>SLL (n = 17)</th>
<th>MCL (n = 16)</th>
<th>Marginal Zone (n = 1)</th>
<th>Total (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>23 (96%)</td>
<td>17 (100%)</td>
<td>12 (75%)</td>
<td>1 (100%)</td>
<td>51 (81%)</td>
</tr>
<tr>
<td>CR</td>
<td>17 (71%)</td>
<td>9 (53%)</td>
<td>6 (38%)</td>
<td>0 (0%)</td>
<td>22 (35%)</td>
</tr>
<tr>
<td>PR</td>
<td>6 (25%)</td>
<td>8 (47%)</td>
<td>4 (25%)</td>
<td>1 (17%)</td>
<td>19 (30%)</td>
</tr>
</tbody>
</table>

- Median duration of PFS: 30 months
- Median OS: 65 months


Radiolabeled Anti-CD20 Antibodies

- Yttrium-90 ibritumomab tiuxetan (Zevalin®)
- Iodine-131 tositumomab (Bexxar®)
- Pretargeted (investigational)
  - Secondary agent to amplify radiation dose and enhance specificity

Common Themes Regarding Radiolabeled Anti-CD20 Antibodies

- Treatment done in a week (2 injections)
- Gamma camera imaging or counts a component
- Manageable radiation safety issues
- Toxicity is principally infusion-related and hematologic
  - Baseline hematologic status relevant
  - Blood count monitoring required for 3 months
- Important long-term toxicity usually absent
- RR, 60%-80%; CR, 30%
- Some patients have durable remissions
- Myeloablative therapy promising

ARS Question 2

Please record your answer on your evaluation form now.

Where should you consider the use of radioimmunotherapy (RIT) in NHL?

A. Relapsed low-grade/transformed NHL
B. Chemotherapy-refractory low-grade NHL
C. Rituximab-refractory low-grade NHL
D. Transformed NHL
E. All of the above
ARS Question 2

Where should you consider the use of radioimmunotherapy (RIT) in NHL?
A. Relapsed low-grade/transformed NHL
B. Chemotherapy-refractory low-grade NHL
C. Rituximab-refractory low-grade NHL
D. Transformed NHL
E. All of the above

Radioimmunotherapy (RIT) for NHL

- Current data clearly support use in:
  - Relapsed low-grade/transformed NHL
    - Advantages over rituximab + chemotherapy debatable
  - Chemotherapy-refractory low-grade NHL
  - Rituximab-refractory low-grade NHL
  - Transformed NHL
  - Responsive disease but with short remissions
- Potential utility in:
  - Upfront therapy (alone or in sequence with chemotherapy)
  - Relapsed/refractory patients with other histologies

Remission Duration of Patients Receiving ASCT for FL in Second or Later Remission

[Graph showing remission duration]
Case Discussion Continued:

- Our patient (now 64 years old) with follicular, grade 2 NHL with local disease status post R-CHOP × 6 cycles, relapsed 2.5 years later, and received bendamustine + rituximab; he had a partial response for 15 months and now presents with 2-cm diffuse LAN, asymptomatic.
- Platelet count is 90,000, and bone marrow biopsy shows 30% involvement of the intertrabecular space with FL cells; LDH is normal, as are blood chemistries.
- He is interested in nonchemotherapeutic and/or investigational approaches.

LAN = Lymphadenopathy

ARS Question 3

The preferred management for this patient is:
A. Novel anti-CD20 antibody
B. Lenalidomide
C. Proteosome inhibitor
D. PI3 kinase inhibitor
E. Bruton’s tyrosine kinase (Btk) inhibitor
F. RIT
G. RICE or similar regimen, followed by ASCT

All the answers except RIT are reasonable options for the management of this patient. RIT is not a reasonable option for a Patient with a platelet count of 90,000 and 30% marrow involvement.
Comparison of Novel Anti-CD20s

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Specificity</th>
<th>Activity (vs Rituximab)</th>
<th>Additional Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofatumumab</td>
<td>IgG2 Human</td>
<td>++ ++ ++ ++ = = ++ =</td>
<td>Binds small extracellular part of CD20; completely human; slower off-rate</td>
</tr>
<tr>
<td>PRO131921</td>
<td>IgG1 Humanized ++ ++ ++ = =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tositumomab</td>
<td>IgG1 Humanized ++ ++ ++ = =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>IgG1 Humanized ++ ++ ++ = =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tositumomab</td>
<td>IgG1 Humanized ++ ++ ++ = =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>IgG1 Humanized ++ ++ ++ = =</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Type: I = immunoglobulin; CDC = complement-dependent cytotoxicity; ADCC = antibody-dependent cellular cytotoxicity.


Ofatumumab

- Human CD20 monoclonal antibody that binds to membrane-proximal epitope encompassing both the small loop and large loop of CD201,2
- Approved in refractory CLL
- Phase III study in relapsed or refractory FL3
  - ORR: 42%
  - Median duration of response: 30 months
  - ORR in prior rituximab-treated patients: 64%


CLL = chronic lymphocytic leukemia

Ofatumumab in Relapsed/Refractory FL—Response Rates

- 87% and 91% of patients in the 500-mg and 1000-mg groups, respectively, completed all 8 infusions of ofatumumab
- No difference in primary endpoint (ORR) between the 500-mg and 1000-mg groups; thus, 2 groups were combined for secondary endpoint analyses

Hagenbeek et al. ASH 2009.
GA101: Mechanisms Of Action—Type I Versus Type II Antibodies

- Increased direct cell death
  - Unique type II epitope and elbow-hinge modification
- Increased ADCC
  - Via increased affinity to the “ADCC receptor” FcgRIIIa

B cell

- Lower CDC activity
  - Due to recognition of type II epitope

Open-label, Phase II, Randomized Study of GA101 vs Rituximab

- Relapsed CD20+ iNHL
- Prior response ≥6 months to last rituximab regimen

**INDUCTION**
- Rituximab 375 mg/m² IV qwk × 4
- GA101 1000 mg IV qwk × 4

**MAINTENANCE**
- Rituximab 375 mg/m² IV q2mo × 12
- GA101 1000 mg IV q2mo × 12

GA101 Versus Rituximab: Best Overall Response by in FL Patients

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Rituximab (n = 75)</th>
<th>GA101 (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>35 (46.7)</td>
<td>45 (60.8)</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>15 (20.0)</td>
<td>20 (27.0)</td>
</tr>
<tr>
<td>PR</td>
<td>20 (26.7)</td>
<td>25 (33.8)</td>
</tr>
<tr>
<td>Difference in ORR, % [95% CI]</td>
<td>14.1 [-2.5; 30.8]</td>
<td></td>
</tr>
<tr>
<td>P-value (1-sided, χ² test)</td>
<td>.04</td>
<td></td>
</tr>
</tbody>
</table>
Emerging Strategies in Relapsed/Refractory Non-Hodgkin’s Lymphoma

PFS Assessed by Investigators in FL Patients

IMIDs in Lymphoid Malignancies

Thalidomide’s Various Effects in Myeloma

Lenalidomide for Relapsed/Refractory Indolent Lymphoma

PFS for Patients Receiving Lenalidomide + R

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Program Slides 15
Single-agent Bortezomib in Relapsed Indolent Lymphoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Subtype</th>
<th>evaluable Patients (N)</th>
<th>CR/CRu</th>
<th>PR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Connor, 2005</td>
<td>FL</td>
<td>9</td>
<td>1/1</td>
<td>5</td>
<td>7 (77%)</td>
</tr>
<tr>
<td></td>
<td>MZL</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td></td>
<td>SLL</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Goy, 2005</td>
<td>FL</td>
<td>5</td>
<td>0/1</td>
<td>0</td>
<td>1 (20%)</td>
</tr>
<tr>
<td></td>
<td>SLL</td>
<td>4</td>
<td>1/0</td>
<td>0</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Strauss, 2006</td>
<td>FL</td>
<td>11</td>
<td>0</td>
<td>2</td>
<td>2 (18%)</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>2 (40%)</td>
</tr>
</tbody>
</table>

WM = Waldenström’s macroglobulinemia.

Promising New Agents in FL

- Antibodies
  - New anti-CD20
  - Anti-CD22, CD80, CD30, CD40, other targets
- Immunostimulatory molecules
- Other categories
  - Proteosome inhibitors
  - mTOR inhibitors
  - PI3K inhibitors (CAL-101)
  - IMIDs (lenalidomide)
  - Btk inhibitors (PCI-32765)

mTOR = mammalian target of rapamycin; PI3 = phosphoinositide-3-kinase.

B-cell Receptor Signalling and Inhibition in B-cell Malignancies

CAL-101 is an orally bioavailable small molecule that inhibits PI3K Delta potently and selectively.

Class I PI3K Isomorph 

<table>
<thead>
<tr>
<th>Activity</th>
<th>EC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGF-induced pAKT</td>
<td>&gt;20,000</td>
</tr>
<tr>
<td>LPA-induced pAKT</td>
<td>1900</td>
</tr>
<tr>
<td>SFL-induced CD63+</td>
<td>3000</td>
</tr>
<tr>
<td>Fog1-induced CD63+</td>
<td>8</td>
</tr>
</tbody>
</table>

- Selective relative to Class I PI3K isomers involved in insulin signaling and other physiological functions
- No off-target activity against Class II or III PI3K, mTOR, or DNA-PK
- No off-target activity seen in screen of >350 protein kinases (Ambit KINOMEscan™)

Single-agent CAL-101 has significant antitumor activity in patients with indolent NHL and CLL.

Combination therapy had effects on lymphadenopathy in all evaluable patients with indolent NHL receiving CAL-101 + B or R.
Phase I Study of the Btk Inhibitor, PCI-32765, in Relapsed/Refractory B-cell Malignancies

- Btk is a downstream mediator of B-cell receptor signaling
- Dosing: 1.25 mg/kg/d, with escalation to 2.5, 5.0, 8.3, 12.5, 17.5 mg/kg
- 29 patients have been enrolled on cohorts 1-4 (12 FL, 7 CLL/SLL, 4 DLBCL, 4 MCL, 2 MZL)
- One DLT (neutropenia); most AEs have been less than grade 2

<table>
<thead>
<tr>
<th>Response</th>
<th>Patients (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>42%</td>
</tr>
<tr>
<td>CR</td>
<td>1 (SLL)</td>
</tr>
<tr>
<td>PR</td>
<td>7 (4 CLL/SLL, 2 MCL, 1 FL)</td>
</tr>
</tbody>
</table>

DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; AEs = adverse events.

Advani et al. ASCO 2010 (abstract 8012).

One Approach to Treat a Patient With Recurrent FL Post First-line Chemotherapy Needing Treatment

- Late relapse (>2 years or so)
  - Many options; decision based on tolerability/efficacy balance
- Early relapse (<2 years or so)
  - Chemotherapy
  - RIT
  - SCT
  - Novel/investigational agents

Managing Patients with Mantle Cell Non-Hodgkin Lymphoma
Case 2

- 56-year-old male who presents with diffuse lymphadenopathy and splenomegaly
- Biopsy shows diffuse MCL
- MIPI score: intermediate
- He received R-hyperCVAD/MTX/cytarabine, followed by ASCT
- Relapse in same areas 8 years later

MIPI = Mantle Cell International Prognostic Index; R-hyperCVAD = rituximab–hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; MTX = methotrexate.

CT Scan at Diagnosis

Case Study: Pathology

MCL showing germinal center overrun by broadened mantle zone in lymph node
The MIPI

- 4 factors independently associated with OS
  - Age
  - PS
  - LDH
  - WBC
- Risk distribution
  - Low: 44% (score: <5.7)
  - Intermediate: 35% (score: 5.7-6.2)
  - High: 21% (score: >6.2)

Survival After Diagnosis by MIPI

WBC = white blood count; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.

Formula for calculating MIPI:

\[ 0.03535 \times \text{age (years)} + 0.6978 \times \text{ECOG > 1} + 1.367 \times \log_{10}(\text{LDH/ULN}) + 0.9393 \times \log_{10}(\text{WBC count}) \]

Simplified MIPI

- 0-3 points applied for each prognostic factor; sum reflects MIPI score
  - Low risk: 0-3 points
  - Intermediate risk: 4-5 points
  - High risk: 6-11 points

Points | Age (y) | ECOG | LDH/ULN | WBC (cells/mm\(^3\))
-------|--------|------|---------|------------------
0       | <50    | 0-1  | <0.67   | <6700
1       | 50-59  |      | 0.67-0.99| 6700-9999
2       | 60-69  | 2-4  | 1.00-1.49| 10,000-14,999
3       | ≥70    |      | ≥1.50   | ≥15,000

MCL

- 5%-10% of B-cell NHLs, with moderately aggressive course
- 74% male; median age, 63 years
- >80% stage III/IV, including marrow involvement
- Extranodal sites common: lymphomatous polyposis, gastrointestinal, soft tissue, or leukemic phase
- Prognosis poor: chemoresponsive, but median survival 30 months with CHOP-type chemotherapy

Front-line Chemotherapy Options for Patients With MCL

- Less intensive
  - R-CHOP
  - Modified HyperCVAD
  - R-CHOP/RIT
  - R-Bendamustine

- More intensive
  - R-CHOP/ASCT
  - R-HyperCVAD/MTX/Ara-C
  - R-HyperCVAD/MTX/Ara-C/ASCT
  - Nordic

ARS Question 4
Please record your answer on your evaluation form now.

What second-line therapy would you choose for this patient (now age 64 years)?

A. Purine analogue–based regimen
B. Bortezomib ± rituximab
C. Lenalidomide
D. Bendamustine-based regimen (BR, BVR)
E. Experimental therapy

All the answers are reasonable choices for this patient. The patient was put on a bendamustine-based regimen.
Recommendations for Second-line Therapy

- Suggested regimens or radiotherapy or clinical trial

<table>
<thead>
<tr>
<th>Suggested Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine ± R</td>
</tr>
<tr>
<td>Bortezomib ± R</td>
</tr>
<tr>
<td>Cladribine ± R</td>
</tr>
<tr>
<td>Fludarabine-based regimen: FC ± R, FCWR, FMR</td>
</tr>
<tr>
<td>Lenalidomide ± R</td>
</tr>
<tr>
<td>PCR</td>
</tr>
<tr>
<td>PEPC ± R</td>
</tr>
</tbody>
</table>

- Second-line consideration of allogeneic transplantation

Fludarabine-based regimens: FC ± R, FCWR, FMR

Second-line Therapy for MCL

- Purine analogue–based regimen
  - ORR: 50% to 70%
- Bortezomib ± rituximab
  - ORR: 30% to 50%
- Lenalidomide
  - ORR: 30% to 50%
- Bendamustine-based regimen (BR, BVR)
  - ORR: 50% to 70%
- Experimental therapy

Bendamustine, Bortezomib, and Rituximab

- Phase II, multicenter study
- Patient population: relapsed, indolent B-cell, or mantle cell NHL
- Exclusion: prior ASCT or RIT within 4 months; prior allogeneic SCT at any time
- Schema: 28-day cycle

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 4</th>
<th>Day 8</th>
<th>Day 11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bendamustine 90 mg/m²</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Rituximab 375 mg/m²</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib 1.3 mg/m²</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Response by Histology**

<table>
<thead>
<tr>
<th>Category</th>
<th>Response Rate % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular NHL</td>
<td>93% (69-99%)</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>71% (36-92%)</td>
</tr>
</tbody>
</table>

Friedberg et al.  Blood 117 (10) 2801-12

**ARS Question 5**

*Please record your answer on your evaluation form now.*

What are the major acute toxicities associated with the BVR regimen?

A. Anemia, thrombocytopenia, neutropenia
B. Peripheral neuropathy
C. Secondary malignancies
D. A and B
E. A, B, and C

**ARS Question 5**

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E. A, B, and C
Monitoring After BVR

- Major acute toxicities
  - Anemia, thrombocytopenia, neutropenia
  - Peripheral neuropathy
  - Nausea/vomiting, diarrhea
- Long-term toxicities (>1 month off chemotherapy)
  - Prolonged thrombocytopenia
  - Peripheral neuropathy

Case Discussion Continued: Relapse #2

- The patient stays in partial remission for 9 months and then has a progression in multiple lymph node sites
- He is considering several clinical trials
  - Lenalidamide ± rituximab
  - Cal-101
  - PCI-32765

Rituximab in Combination With Lenalidomide in MCL*

- Phase I/II study in relapsed/refractory MCL
- MTD: lenalidomide 20 mg plus rituximab 375 mg/m²

<table>
<thead>
<tr>
<th>Objective Response</th>
<th>% (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>70% (7/10)</td>
</tr>
<tr>
<td>CR</td>
<td>30% (3/10)</td>
</tr>
<tr>
<td>PR</td>
<td>40% (4/10)</td>
</tr>
<tr>
<td>SD</td>
<td>10% (1/10)</td>
</tr>
<tr>
<td>Response duration</td>
<td>8 months</td>
</tr>
</tbody>
</table>

CAL-101 is an orally bioavailable small molecule that inhibits PI3K Delta potently and selectively.

Class I PI3K Isomers

<table>
<thead>
<tr>
<th>Activity</th>
<th>EC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGF-induced pAKT</td>
<td>&gt;20,000</td>
</tr>
<tr>
<td>LPA-induced pAKT</td>
<td>1900</td>
</tr>
<tr>
<td>RBL-P-induced CD63+</td>
<td>3000</td>
</tr>
<tr>
<td>FcgR1-induced CD63+</td>
<td>8</td>
</tr>
</tbody>
</table>

- Selectivity relative to Class I PI3K isoforms involved in insulin signaling and other physiological functions
- No off-target activity against Class II or III PI3K, mTOR, or DNA-PK
- No off-target activity seen in screen of >350 protein kinases (Ambit KINOMEscan™)

Cal-101 in B-cell Lymphoma Best Response

PCI-32765
Novel Small-molecule Btk Inhibitor

- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent Btk inhibition
  - IC50 = 0.5 nM
- Orally available
- Once-daily dosing results in 24-hour sustained target inhibition
Oncology Exchange
Emerging Strategies in Relapsed/Refractory Non-Hodgkin’s Lymphoma

Best Response

- BTZ-naive (n = 31)
  - CR: 71%
  - PR: 16%
  - SD: 13%
  - PD: 10%

- BTZ-exposed (n = 20)
  - CR: 65%
  - PR: 19%
  - SD: 15%
  - PD: 11%

- Total (n = 51)
  - CR: 69%
  - PR: 16%
  - SD: 14%
  - PD: 15%

*Wang et al. ASH 2011; Abstract 442

Second-line Therapy Options for MCL

- Evaluate age and overall condition of the patient—transplantation-eligible?
- Standard options
  - Purine analogue
  - Bendamustine
  - Bortezomib
  - Autologous or allogeneic SCT in CR2
- Investigational options
  - Lenalidamide
  - BCR pathway agents

Thank you for joining us today!

Please remember to turn in your evaluation form.
Your participation will help shape future CME activities.