New Pathways, New Targets and New Therapies for NHL: CHOPping Away

David Frame, PharmD
Hematology/Oncology/BMT Clinical Specialist
University of Michigan Health System
Assistant Professor of Pharmacy
University of Michigan
Ann Arbor, Michigan

Educational Objectives

• Identify the different types of NHL
• Describe changes in the genetic makeup of different types of NHL and how this could be used for therapeutic decision making
• Explore the current guideline recommendations for the treatment NHL
• Differentiate mechanisms of action as well as efficacy and safety data that support the use of new and emerging agents for the treatment of NHL
• Utilize pharmacologic principles of therapeutic agents to develop rationales for treatment

Types of Non-Hodgkin Lymphoma (NHL)

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>25%</td>
</tr>
<tr>
<td>Small lymphocytic</td>
<td>7%</td>
</tr>
<tr>
<td>MALT type marginal zone B cell</td>
<td>7.5%</td>
</tr>
<tr>
<td>Nodal type marginal zone B cell</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Lymphoplasmacytic</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Diffuse large B cell</td>
<td>32%</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>90%</td>
</tr>
<tr>
<td>Burkitt</td>
<td>2.5%</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>6%</td>
</tr>
</tbody>
</table>


Indolent NHL

• Follicular lymphoma (FL) is 70% of this group
• Other entities in this group include:
  • Small lymphocytic lymphoma (SLL)/ Chronic lymphocytic Leukemia (CLL)
  • Lymphoplasmacytoid lymphoma
  • Marginal zone lymphomas (MALT, nodal or extranodal)

Therapies Based on Stage

• Indolent stage I and contiguous stage II NHL
  • Radiation therapy (2500–4000 cGy)
  • 10-year failure-free survival rate of 50%–60%, with overall survival (OS) 60%–80%

• Indolent noncontiguous stage II, III, and IV NHL
  • R-CHOP (R-miniCHOP if >80 years old) or RCVP
  • Overall response rate (ORR): 95%
  • Progression-free survival (PFS): 40 months

NCCN Guidelines Vs 4, 2018, Last Update May 15, 2018

Changes From R-CHOP

- Rituximab-Bendamustine vs R-CHOP
  - BR superior for PFS (Not Reached vs 41 months (p=0.0072)
  - BR better tolerated
- Maintenance Rituximab for 4 yrs no better than 2 yrs after BR


RELEVANCE: Phase III Rituximab-Lenalidomide vs R-Chemo

- Previous untreated patients with advanced FL requiring treatment per GELF criteria (N = 1030)
  - Lenalidomide*: 20 mg PO QD Days 2-22, 28-day cycles (18 cycles) + Rituximab
  - Chemotherapy (choice of CHOP, B, or CVP) + Rituximab† (n = 517)


- Total tx duration up to 120 wks

Obinutuzumab

- FDA approved for previously untreated stage II bulky, III, or IV FL:
  - In combination with chemotherapy
  - Followed by obinutuzumab monotherapy in patients achieving at least a PR

- Dose for FL is:
  - 1000 mg on days 1, 8, and 15 of cycle 1
  - 1000 mg on day 1 of cycles 2-6 or cycles 2-8
  - Then 1000 mg every 2 months for up to 2 years

Gazyva (Obinutuzumab) Package Insert, Genentech 11/2017


GALLIUM Trial: Chemotherapy + Obinutuzumab or Rituximab

- 1202 patients with previously untreated FL
- Chemotherapy (CHOP, CVP, or bendamustine) for 6-8 cycles + obinutuzumab or rituximab

HR for progression, relapse, or death, 0.66 (95% CI, 0.51–0.85) P=0.001

GALLIUM Trial: Safety

- Obinutuzumab arm had higher incidences of serious adverse reactions
  - ARs: 50% versus 43%
  - Grade ≥3 ARs: 79% versus 72%
  - Fatal infections: 2% versus <1%
- Most common grade ≥3 ARs (incidence, ≥5%) observed more frequently with obinutuzumab were neutropenia, febrile neutropenia, thrombocytopenia, and infusion reactions
- Recipients of bendamustine had higher incidences of serious and fatal infections than recipients of CHOP or CVP


Targeting the B-cell Receptor

Adapted from Camisi et al. Molecular Cancer (2015) 14:207

Idelalisib in Relapsed Indolent Lymphoma


Copanlisib

- For the treatment of adult patients with relapsed FL who have received at least 2 prior systemic therapies
- 60 mg administered as a 1-hour intravenous infusion on days 1, 8, and 15 of a 28-day cycle
  - Dose 45 mg with strong CYP3A inhibitors
  - Continue treatment until disease progression or unacceptable toxicity

Aliqopa (Copanlisib) PI, Bayer Healthcare Pharmaceuticals 9/2017

Copanlisib Efficacy

ORR 59% (CR14%)

Copanlisib Induced Hyperglycemia

- Grade 3 or 4 hyperglycemia (blood glucose ≥250 mg/dL) occurred in 41% of patients
- Serious hyperglycemic events occurred in 2.8% of patients
- Generally infusion-related hyperglycemia
- Blood glucose levels typically peaked 5–8 hours post-infusion and subsequently declined to baseline
- Blood glucose levels remained elevated in 17.7% of patients 1 day after
- For Pre- or post-dose glucose 500 mg/dL or more, hold dose until fasting glucose is 160 mg/dL or less and:
  - First occurrence: reduce dose from 60 mg to 45 mg
  - Subsequent occurrences: reduce dose from 45 mg to 30 mg
  - If persistent at 30 mg, discontinue

Factors That May Impede Adherence

- Financial burden, inadequate insurance coverage
- Dissatisfaction with efficacy
- Side effects
- Perception of being cured
- Dislike being reminded of illness
- Don’t believe will work as well as IV chemo
- Do not understand their regimen
- Confusion about medication schedules
- Do not understand the gravity of nonadherence
- Lack of symptoms or negative effects following nonadherence

Rituximab and Hyaluronidase Subcutaneous

- For adult patients after 1 dose of rituximab
- FL
  - Relapsed or refractory FL as a single agent
  - Previously untreated FL, in combination with first-line chemotherapy
  - Maintenance therapy, after CR or PR to rituximab, in combination with chemotherapy
  - Non-progressing or SD as a single agent after CVP chemotherapy
- Diffuse Large B-cell lymphoma (DLBCL)
  - Previously untreated in combination with CHOP or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia (CLL)
  - Previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide (FC)

Response versus Rituximab DLBCL

<table>
<thead>
<tr>
<th></th>
<th>Rituximab/Hyaluronidase (n=287)</th>
<th>Rituximab (n=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response Rate (CR/CRu)</td>
<td>179 (47% [42;52])</td>
<td>82 (42% [39;45])</td>
</tr>
<tr>
<td><strong>Difference in response rates (95% CI)</strong></td>
<td>4.9% [-0.8;13.5]</td>
<td></td>
</tr>
<tr>
<td>Progression-Free Survival</td>
<td>Number of patients with event</td>
<td>104 (27%)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI) (unstratified Cox model)</td>
<td>1.22 [0.85-1.73]</td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>Number of patients with event</td>
<td>63 (17%)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI) (unstratified Cox model)</td>
<td>1.08 [0.70;1.64]</td>
<td></td>
</tr>
</tbody>
</table>

Aggressive NHL

- Diffuse large B-cell lymphoma (DLBCL)
- Mantle cell lymphoma (MCL)
- Immunoblastic large-cell
- Anaplastic large-cell
- Lymphoblastic large-cell
- Burkitt and Burkitt-like lymphomas (high-grade lymphomas)
DLBCL: Germinal Center B Cell-Like (GCB) versus Activated B Cell-Like (ABC)

In ABCs, cells differentiate appropriately into plasma cells. Once differentiated, the B cell surface receptors become overstimulated. This leads to constant stimulation of NF-κB and potential overexpression of MYC or BCL2.

GCB cells do NOT differentiate appropriately. During the germinal phase of creating unique plasma cells, mutations occur. Thus, it is a common idea that mutated DNA creates mutated cells.

DLBCL: ABC Future Therapies

- R²-CHOP
  - Lenalidomide 25 mg orally days 1–10
  - R-CHOP days 1–5

DLBCL: Genetics

- MYC
  - Normally a transcription regulator
  - Abnormalities cause aberrant and aggressive DNA transcription and cell proliferation
- BCL2
  - Normally sequesters BIM and BAX, proteins responsible for triggering mitochondria-induced apoptosis
  - Aberrant and aggressive expression of BCL2, prevents cell apoptosis
- BCL6
  - BCL6 is noted to help regulate BCL2 and MYC expression
  - Abnormalities in BCL6 can dysregulate BCL2 and MYC

DLBCL: GCB Treatment

- If Double Hit or Triple Hit:
  - R-DA-EPOCH
  - Equilibrates the survival of DHL and non-DHL GCBs receiving R-CHOP
  - Consider CNS prophylaxis
  - Consider Consolidation with Autologous Transplant

- If any other GCB:
  - R-CHOP
  - Rituximab 375 mg/m² on day 1
  - Cyclophosphamide 750 mg/m²/1000 IU on day 1
  - Doxorubicin (hydroxydaunorubicin) 50 mg/m²/day 1
  - Vincristine (Oncovin) 1.4 mg/m²/day 1 (capped dose at 2 mg)
  - Prednisone 40 mg/m² PO BID days 1–5

OUTCOMES of R-CHOP
Better for GCB than ABC

Dunleavy K, Clin Cancer Res; 20(20); 5182–93.

DLBCL: Double Hit Lymphoma (DHL)
- Genetic abnormalities in MYC and BCL2 in GCBs
- Double Expresser Lymphoma (DEL)
  - Expression of MYC and BCL2 with intact DNA in ABCs
  - If BCL6 is also highly expressed, the lymphoma may be noted as a triple hit

DLBCL: Genetics

- Double Hit Lymphoma (DHL)
  - Genetic abnormalities in MYC and BCL2 in GCBs
  - Double Expresser Lymphoma (DEL)
    - Expression of MYC and BCL2 with intact DNA in ABCs
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Dunleavy K, Clin Cancer Res; 20(20); 5182–93.

New Method To Predict Outcomes 
Circulating Tumor DNA (ctDNA) 
Kurti B, JCO 2018:8:6-1 
CHOP BASED 1 LINE REGIMEN 
SALVAGE THERAPY FOR R/R/ Disease 
Early Molecular Response Predicts EFS 
Chimeric Antigen Receptor (CAR) T Cells 
Axicabtagene Ciloleucel 
DLBCL Duration of Response 
Axicabtagene Ciloleucel: DLBCL Overall Survival 
More than one half of patients with PR progressed by Month 3, defining Month 3 as a clinically relevant timepoint 
Axicabtagene Ciloleucel: DLBCL Overall Survival 
CAR: Modular Design 
Targeting Element (scFv) 
Spacer 
Transmembrane Domain 
Co-stimulatory Domain 
Signaling Domain 

ZUMA-1 Long-term Follow-up

- ORR and CR rate increased during long-term follow-up, with patients achieving CRs up to 1 yr after a single infusion of axi-cel.
- Patients with an ongoing response at 3 months had ~80% probability of maintaining response at 12 months.
- Achieving PR or CR by 3 months may be prognostic of long-term response to axi-cel.

Cytokine Release Syndrome

- Symptoms may be mild:
  - Flu-like, fever/myalgia
- Potential severe inflammatory syndrome:
  - Capillary leak
  - Pulmonary edema
  - Hypotension
  - Coagulopathy (DIC)
  - Multi-organ system failure
- Usually occurs within 1–14 days after infusion.

Axicabtagene Ciloleucel: DLBCL Adverse Events

<table>
<thead>
<tr>
<th>Adverse Drug Reactions (n=101)</th>
<th>Any Event*</th>
<th>Cytokine Release Syndrome†</th>
<th>Neurologic‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Grade: 101 (100%)</strong></td>
<td>Grade 1–2: 5 (5%)</td>
<td>Grade 0: 96 (95%)</td>
<td>Grade 1–2: 61 (60%)</td>
</tr>
<tr>
<td><strong>Any Grade: 94 (93%)</strong></td>
<td>Grade 1–2: 61 (60%)</td>
<td>Grade 0: 13 (13%)</td>
<td>Grade 0: 28 (28%)</td>
</tr>
</tbody>
</table>

*Grade ≥3 incidence ≥20%: neutropenia, anemia, thrombocytopenia, febrile neutropenia, encephalopathy, thrombocytopenia.
†Neurologic events used in 17 (17%) (RMH 1.2) of patients; median onset CRS: 2 days (range, 1–12); median time until resolution: 8 days.
‡Median onset of neurologic events: day 5 (range, 1–17); median resolution: day 17.

Tisagenelecleucil

Juliet Trial 14 month Follow-up

- Overall response rate was 52%, CR=40%.
- Of the patients in CR at month 3, 83% remained in CR at month 12, and the median duration of response was not reached at 14 months.
- 54% of patients who had achieved a PR converted to CR.
- Patients had a 65% chance of being relapse-free one year after onset of response.
- With eight months of additional follow-up, response rates remained consistent with previous reports and the safety profile was maintained with no emergence of new safety signals.

R-HyperCVAD in MCL First-Line: Long-Term Update (FFS and OS)

- Median follow-up: 84 months (7 years).

Mantle Cell Lymphoma (MCL)

- European Hematology Association (EHA 2018) Abstract # S799
Nordic Group: MCL Autologous HCT Studies

**MCL1:**
- Cyclophosphamide 200 mg/m² on day 1 +
- Doxorubicin 75 mg/m² on day 1 +
- Prednisone 100 mg on day 1 - 5 +
- BEAM/BEAC + PBSCT

**MCL2:**
- MCL1 alternating with
  - Ara-C 3 g/m² BID on days 1 and 2 +
  - Rituximab 375 mg/m² on days 1 and 9 +
- BEAM/BEAC + PBSCT

**Agoraphobia and MCL**

**HD Cytarabine Adds Significant Benefit**

**R-Maxi-CHOP alternate R-cytarabine: BEAM or BEAC**

**Rituximab Maintenance after AutoBMT**

**Phase III LyMa trial**

- Rituximab Maintenance 375 mg/m² every 2 months for 3 years vs Placebo
- 4yr EFS was 78%. Rituximab vs G1% (HR=0.46, p=0.0016)
- 4 yr PFS 82% Rituximab vs 65% (HR 0.4, p=0.0007)
- 4 yr OS 89% Rituximab vs 81 % HR +0.5, p=0.04

**Progression-Free Survival (Primary Endpoint)**

- B-R superior to R-CHOP for PFS in MCL
  - 35 months versus 22 months
  - P=0.0044

**First-Line Bendamustine + Rituximab in Patients with MCL**

- **Bendamustine + Rituximab**
  - CR, 50%; CR, 60%
  - PFS: 18 months
- **Bortezomib**
  - ORR, 33%; CR, 8%
  - Median time to progression: 6.7 months
- **Lenalidomide + Rituximab**
  - ORR, 57%; CR, 36%
  - Median duration of response: 18.9 months

**Relapsed/Refractory MCL**

- Bendamustine-Rituximab
  - ORR, 50% CR, 60%
  - PFS: 18 months
- Bortezomib
  - ORR, 33%; CR, 8%
  - Median time to progression: 6.7 months
- Lenalidomide-Rituximab
  - ORR, 57%; CR, 36%
  - Median duration of response: 18.9 months
Targeting the B Cell Receptor

Ibrutinib in Relapsed/Refractory MCL

Adapted from Camicia et al. Molecular Cancer (2015) 14:207


Acalabrutinib

- Indicated for the treatment of adult patients with MCL who have received at least 1 prior therapy
- 100 mg q12h PO until disease progression or unacceptable toxicity
- Swallow capsule whole with water, with or without food
- No PPI
- No dosing available for strong CYP3A4 inducer/inhibitor
- Itraconazole showed 5-fold increase

Calquence Package Insert, AstraZeneca 2017

Warnings

- Hemorrhage: monitor for bleeding and manage appropriately
- Infections: monitor patients for signs and symptoms of infection and treat as needed
- Cytopenias: monitor complete blood counts monthly during treatment
- Second Primary Malignancies: other malignancies have occurred in patients, including skin cancers
- Atrial Fibrillation and Flutter: monitor for atrial fibrillation and atrial flutter and manage as appropriate

Calquence Package Insert, AstraZeneca 2017

Acalabrutinib: Results in MCL

Calquence Package Insert, AstraZeneca 2017

Prognosis

- Population
  - 45% of patients were 65 years or older
  - 46% were found to have stage III disease.
  - Most had PTCL-NOS (51.3%), AITL (26.0%), ALC (22.7%) with more ALK− (79%) than ALK+ (21%).
- General Outcomes
  - Median time to relapse or progression after primary therapy was 6.7 months
  - Median progression-free survival after relapse 3.1 months
  - Median OS after relapse 5.5 months

Targets for T cell Lymphomas

New Combinations

- Epigenetic dysfunction, mutations in TET2, DNMT3A, and IDH2
- HDAC Inhibitors
  - Romidepsin + Palbociclib: ORR 71%, CR 29%, PFS 4.4 mo, OS 12.4 mo
  - Romidepsin + Duvelisib: CR 50%
  - Romidepsin + CHOP: ORR 68%, PFS at 18 months of 5.7%, OS at 18 mo 77%
  - Panobinostat + Decitabine
- CD30
  - Brentuximab + CHP: 100% ORR with 88% CR, PFS 1 yr 71%, 1-year OS 88%
  - Brentuximab + Lenalidomide

Summary

- Treatment of non-Hodgkin lymphoma has had several significant changes in the past few years

  - For FL:
    - Bendamustine-rituximab has a better PFS than R-CHOP with fewer toxicities
    - Rituximab maintenance also increases PFS
  - For relapsed/refractory, obinutuzumab, idelalisib, and copanlisib are options

  - For DLBCL:
    - Should be determined if ABC or GCB (with other hits)
      - ABC, R-CHOP; GCB, R-CHOP; GCB with DHL or DEL, DA-EPOCH
    - CAR T cell now available for relapsed/refractory

Additional Resources

- NCCN Guidelines B cell Lymphoma V4 2018, Last Update May 15, 2018

Cutaneous T Cell Lymphoma: Brentuximab Vedotin versus Methotrexate or Bexarotene

<table>
<thead>
<tr>
<th>Brentuximab Vedotin (n=64)</th>
<th>Physician’s Choice (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>15.8 vs 3.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.373 (0.245–0.569); P&lt;0.001</td>
</tr>
</tbody>
</table>

Probability of PFS

Months From Randomization
Pre-Test

Question & Answer Session