Updates in the Treatment of Non-Hodgkin Lymphoma: ASH 2008

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Topics

- Mantle Cell Lymphoma
  - What is the standard of care for younger patients? (abstracts 581, 769, 833, 3050)
  - Other regimens
- New Agents
  - Do vaccines work in FL? (236)
  - Lenalidomide (262, 268)
Active questions in MCL

• Younger patients
  – Are intensive therapies the way to go?
  – If yes, which intensive therapy approach?
    • Conventional R-hyperCVAD with alternating R-MTX/Ara-C?
    • Aggressive cytoreduction followed by ASCT?
      – If yes, does the method of cytoreduction matter?

• Older patients
  – Not addressed today

Conventional R-hyperCVAD update

• Abstract 833: MD Anderson (Romaguera et al)
  – 6 – 8 cycles of R-hyperCVAD alternating with R-MTXAraC
  – 97 pts (65 under ≤ 65y), median follow-up : 84 mo
  – Patients ≤ 65 y
    • 7y FFS : 52%, 7y OS : 68%

• Abstract 3050: Multicenter trial from GISL (Merli et al)
  – N = 32, median age 54
  – 7 patients unable to complete therapy due to toxicity
    • 2 toxic deaths
  – 2 yr FFS 75%
  – Results are similar to SWOG report at ASH 07
    • Efficacious but some issues with tolerability
Early consolidation with myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission of mantle cell lymphoma - Long term follow-up of a randomized trial of the European MCL Network


European MCL Network: ASCT vs. IFN

6x CHOP-like chemotherapy

2 cycles consolidation

Interferon-α maintenance

PR, CR

DexaBEAM (stem cell harvest)

Cyclo 120mg/kg + TBI

autologous PBSCT
European MCL Network: ASCT vs. IFN
Time to treatment failure (ITT)

European MCL Network: ASCT vs. IFN
Overall Survival (ITT)
Conclusions

• ASCT applied in first remission
  – Prolongs the remission durability
  – Appears to favorably impact OS

• Note the “control” arm median OS
  – 5+ yrs despite 1st remission of only 1.5 yrs

• What would happen if a better cytoreduction was used?

MCL Conclusions: younger patients

• Several trials demonstrating median remissions of greater than 5 years with intensive strategies in younger patients

• Conventional hyperCVAD excellent results at MD Anderson
  – Appears unlikely similar results will be realized in 2 multicenter trials

• AutoSCT consolidation prolongs remission and survival in one small RCT from the European MCL consortium

• 2 trials demonstrate outstanding long term outcomes with high dose cytarabine incorporated into induction followed by autoSCT
  – Nordic and GELA
  – Multicenter and ITT

• Ongoing European RCT of R-CHOP vs. R-CHOP/R-DHAP followed by ASCT
VcR-hyperCVAD in First-line MCL: Phase II Study Schema

Untreated MCL (N = 22)

Bortezomib* 1.5 mg/m² IV Days 1, 4
Rituximab 375 mg/m² IV Day 1
Cyclophosphamide 300 mg/m² IV q12h D 1-3
Doxorubicin 50 mg/m² cont inf D 1-2
Vincristine† 2 mg Day 3
Dexamethasone 40 mg po D 1-4
G-CSF with each cycle
6 X 21-day cycles

Consolidation:
Rituximab 375 mg/m² weekly x 4

Maintenance:
Rituximab 375 mg/m² every 3 mos for 5 years

CR, CRu, PR

* Dose adjusted to 1.3 mg/m² for pts 8-22
† Dose adjusted to 1 mg for pts 15-22


VcR-hyperCVAD in First-line MCL: Response and Survival

- Overall response rate 90%
- 2-yr PFS: 75%
- 2-yr OS: 97%
- Median follow-up 23 months

VcR-hyperCVAD in First-line MCL: Toxicity

- 2 dose modifications made due to painful peripheral neuropathy
  - 1/16 pts at final dose level experienced neuropathy
- Thrombocytopenia and neutropenia most frequent hematologic toxicities

<table>
<thead>
<tr>
<th>Grade 3/4 Non-Hematologic Adverse Events,* n</th>
<th>Patients (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>10</td>
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<tr>
<td>Elevated glucose</td>
<td>4</td>
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<tr>
<td>Low sodium</td>
<td>4</td>
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<tr>
<td>Dehydration</td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
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</table>

<table>
<thead>
<tr>
<th>Grade 3/4 Hematologic/Infection Adverse Events,* n</th>
<th>Patients (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>23</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>12</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
</tr>
<tr>
<td>Frebrile neutropenia</td>
<td>5</td>
</tr>
<tr>
<td>Infection without neutropenia</td>
<td>4</td>
</tr>
</tbody>
</table>

*Occurring in > 1 patient.


Topics

- Mantle Cell Lymphoma
  - What is the standard of care for younger patients? (abstracts 581, 769, 833, 3050)
  - Other regimens
- New Agents
  - Do vaccines work in FL? (236)
  - Lenalidomide (262, 268, 3060)
Lenalidomide for Relapsed MCL

- Abstract 262: Zinzani et al.
  - 25 mg/day 1-21 q 28
  - N = 39, median of 3 prior therapies
  - ORR 41% (16/39), SD 26%
  - Median PFS 7.1 months, median RD not reached
  - Grade 3-4 neutropenia 50%, thrombocytopenia 25%

- Abstract 1560: Reeder et al.
  - 14 patients with prior bortezomib
  - ORR 57% (8/14)

Lenalidomide for Relapsed MCL and DLBCL

- Abstract 268: Czuczman et al.
  - N = 73, median 3 prior treatments
  - ORR 29% (21/73), CR 4%
  - Median RD ~ 3-4 months
  - Grade 3-4 neutropenia 32%, thrombocytopenia 15%
  - 2 cases of acute renal failure, 2 acute confusional states

- Lenalidomide has promising activity in recurrent MCL
  - Efficacy more modest in recurrent DLBCL
  - Dose and schedule issues remain
NHL-003: Single Agent Lenalidomide in R/R MCL (Rationale)

- MCL is an aggressive B-cell non-Hodgkin's lymphoma (NHL) with suboptimal responses to conventional chemotherapy
  - Short DOR and limited PFS
- Lenalidomide induces p21 tumor suppressor expression, leading to cell cycle arrest
  - Cyclin D1 overexpression common in MCL
  - Cyclin D1 overexpression relative to p21 predisposes to lenalidomide-induced cell cycle arrest


NHL-003: Single Agent Lenalidomide in R/R MCL (Interim Response Results)

- Patient Population (N = 53)[1]
  - 39 pts evaluable for response
  - ≥ 1 previous treatment
  - ECOG PS ≤ 2
- Study endpoints by International Workshop Lymphoma Response Criteria[2]
  - Primary endpoint
    - ORR
  - Secondary endpoints
    - DOR, PFS, Safety

**NHL-003: Single Agent Lenalidomide in R/R MCL (Interim Safety Results)**

- Cytopenias most frequent grade 3/4 adverse events
- Dose reductions required in 15 patients (38%)
  - Median time to first dose reduction: 1.8 months (range: 0.4-8.4)
  - Most frequently due to neutropenia (52%) and thrombocytopenia (23%)
- Led to treatment discontinuation in 6 patients (15%)

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Patients (n = 39)</th>
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<tbody>
<tr>
<td></td>
<td>Grade 3</td>
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<tr>
<td>Hematologic</td>
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<tr>
<td>Neutropenia</td>
<td>31</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
</tr>
<tr>
<td>Anemia</td>
<td>10</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>8</td>
</tr>
<tr>
<td>Nonhematologic</td>
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<tr>
<td>Fatigue</td>
<td>10</td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
</tr>
<tr>
<td>General deterioration in physical health</td>
<td>3</td>
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</table>


**R2: Preliminary Results of a Phase II Study of Lenalidomide and Rituximab in Relapsed/Refractory Indolent Non-Hodgkin’s Lymphoma (NHL)**

**Treatment**

- Lenalidomide was initiated at a dose of 25 mg administered orally once daily, on days 1–21 of a 28-day cycle, and continued until disease progression.
- Following the development of tumor lysis syndrome (TLS) in the first 2 patients enrolled, the protocol was amended to reduce the starting dose of lenalidomide to 20 mg and TLS prophylaxis was provided.
- Rituximab 375 mg/m2 was infused starting on day 15 of cycle 1 and repeated weekly for a total of 4 doses. If after cycle 2 a patient had less than a CR, 4 additional doses could be administered at the discretion of the treating physician.

R² for Relapsed/Refractory Indolent Non-Hodgkin’s Lymphoma (NHL)

Median PFS is currently ongoing and > 168 days


Phase 3 Trial of Bendamustine + Rituximab vs R-CHOP in First-Line Indolent and Mantle Cell Lymphomas

- Primary end point: To prove a noninferiority of BR vs R-CHOP in EFS (defined as a difference of less than 10% in EFS after 3 years)

Phase 3 Trial of Bendamustine + Rituximab vs R-CHOP in First-Line Indolent and Mantle Cell Lymphomas: Response

- ORR: 94% (BR) vs 83% (R-CHOP)
- CR: 41% (BR) vs 33% (R-CHOP)
- PR: 53% (BR) vs 60% (R-CHOP)

Median follow-up of 28 months.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>End point</th>
<th>BR</th>
<th>R-CHOP</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>EFS (months)</td>
<td>Not reached</td>
<td>39</td>
<td>Not significant</td>
</tr>
<tr>
<td></td>
<td>Death (n)</td>
<td>25</td>
<td>25</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Phase 3 Trial of Bendamustine + Rituximab vs R-CHOP in First-Line Indolent and Mantle Cell Lymphomas: Safety

A Placebo-Controlled Phase III Trial of Patient-Specific Immunotherapy with Mitumprotimut-T (Id-KLH) and GM-CSF Following Rituximab in Patients with CD20+ Follicular Lymphoma


A. Hamlin, MD
Presenting for the FavId-06 Trial Investigators
Background

- Mitumprotimut-T is a patient-specific Id-KLH vaccine in which the Id protein is produced by proprietary recombinant technology (Specifid®, Favriile, San Diego, CA)
- A Phase II trial of mitumprotimut-T + GM-CSF in treatment-naïve and relapsed/refractory follicular B-cell lymphoma patients achieving SD/PR/CR to rituximab has resulted in:
  - late conversions to CR
  - an event-free survival plateau at 4 years, suggesting a vaccine activity
- This Phase III trial was conducted to confirm these results


Phase III Trial Schema

* Each vaccination consists of 1 mL mitumprotimut-T 1 mg or placebo, SQ, Day 1 and Leukine® (GM-CSF) 250 mcg, SQ, Days 1-4, monthly x 6, Q 2 months x 6, then Q 3 months until PD or unacceptable toxicity
**Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Mitumprotimut-T (n = 174)</th>
<th>Placebo (n = 175)</th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>56 (22 - 86)</td>
<td>53 (21 - 81)</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>146 (84%)</td>
<td>152 (87%)</td>
</tr>
<tr>
<td>1</td>
<td>28 (16%)</td>
<td>22 (13%)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>17 (10%)</td>
<td>28 (16%)</td>
</tr>
<tr>
<td>III-IV</td>
<td>155 (89%)</td>
<td>146 (83%)</td>
</tr>
<tr>
<td><strong>B Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>12 (7%)</td>
<td>23 (13%)</td>
</tr>
<tr>
<td><strong>Prior therapy</strong></td>
<td></td>
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<tr>
<td>Treatment-naive</td>
<td>137 (79%)</td>
<td>138 (79%)</td>
</tr>
<tr>
<td>Relapsed/refractory</td>
<td>37 (21%)</td>
<td>37 (21%)</td>
</tr>
<tr>
<td><strong>FLIPI Risk Group</strong></td>
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</tr>
<tr>
<td>Low</td>
<td>51 (29%)</td>
<td>78 (47%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>71 (41%)</td>
<td>66 (38%)</td>
</tr>
<tr>
<td>High</td>
<td>49 (28%)</td>
<td>29 (17%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (2%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

**Time to Progression:**

**Intent-to-Treat (N = 349)**

- Placebo + GM-CSF: TTP 12.6 ms (n=175)
- Mitumprotimut-T + GM-CSF: TTP 9.0 ms (n=174)

HR = 1.384 (95% CI 1.05-1.8); p = .019
Conclusions

- Patient-specific Id-KLH and GM-CSF therapy does not improve TTP, objective response rate, or duration of response in patients with CD20+ follicular lymphoma who achieve SD or an objective response following rituximab.

- Results consistent with another randomized Phase 3 trial in treatment-naïve patients with CD20+ follicular lymphoma who achieve CR/PR following CVP chemotherapy.

- Possible reasons for failure:
  - Immunosuppressive effect of rituximab
  - Id is a weak immunogen
  - Id irrelevant target