How I Treat Mantle Cell Lymphoma

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Outline

• Mantle cell lymphoma review
• Prognostic indices and implications for outcome and treatment
• Selection of approach to untreated patients
Mantle Cell Lymphoma- Background

- < 10% of cases of NHL
- Characterized by:
  - CyclinD1 positivity by IHC
  - Immunophenotype:
    - CD5+, CD20+, CD23-
    - t(11;14)
- Frequently Stage IV
  - Bone Marrow Involvement
  - Peripheral Blood Lymphocytosis
  - Spleen
  - GI Tract

Source: National Cancer Database
MCL International Prognostic Index

Calculated pre-treatment and associated with OS

- WBC Count
- Age
- Performance
- LDH Status

Hoster et al, Blood 2008

Hoster et al, J Clin Oncol 2014
MCL International Prognostic Index

High Risk MIPI associated with better OS in additional series

Eskelund et al, Brit J Haem 2017
Staton et al, ASH 2016
Ki67 Proliferative Index

- Measurable by IHC but can vary within a patient
- Cutoff of 30% frequently utilized

Hoster, J Clin Oncol 2016
<table>
<thead>
<tr>
<th>MIPI-C RISK GROUP</th>
<th>MIPI RISK (Low, Intermediate, or High)</th>
<th>Ki67</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>&lt; 30%</td>
<td>9.4 years</td>
</tr>
<tr>
<td>Low-Intermediate</td>
<td>Low</td>
<td>≥ 30%</td>
<td>4.9 years</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>&lt; 30%</td>
<td></td>
</tr>
<tr>
<td>High-Intermediate</td>
<td>Intermediate</td>
<td>≥ 30%</td>
<td>3.2 years</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>≥ 30%</td>
<td>1.8 years</td>
</tr>
</tbody>
</table>

Ki67 + MIPI: The MIPI-C

Hoster et al, J Clin Oncol 2016
Cytogenetics in MCL

• Complex karyotype (> 3 abnormalities)
  • ~20% of patients
• Associated with inferior PFS in MCL
• Multi-center study in US

 Median OS: 4.5 vs 11.6 years
Median PFS: 1.9 vs 4.4 years

Greenwell et al, Cancer 2018
Genomic Aberrations & Clinical Outcome

TP53 or CDKN2A Deletions – RCHOP/RDHAP

TP53 mutation – Nordic MCL2/3

- TP53 likely important and associated with poor prognosis
- Assessment of individual abnormalities challenging and of questionable utility
- New genes and associated prognostic importance continue to be identified
- Multi-gene panel needed to better integrate prognostic importance of individual abnormalities

“Traditional” Approach to Treatment

New Dx – Confirm Diagnosis and Complete Staging /Prognostic Work-up

Candidate for Transplant?

Yes

“Intensive” Induction therapy

Autologous Transplant

No

“Less Intensive” Induction therapy

Maintenance

Observation
# My general approach and considerations

<table>
<thead>
<tr>
<th>&lt; 60 and Healthy</th>
<th>60-70 and Healthy</th>
<th>70+ and Healthy</th>
<th>Frail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considerations:</td>
<td>Considerations:</td>
<td>Considerations:</td>
<td>Considerations:</td>
</tr>
<tr>
<td>• Symptoms</td>
<td>• Symptoms</td>
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<tr>
<td>• Stage / Tumor Burden</td>
<td>• Stage / Tumor Burden</td>
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<tr>
<td>• Prognostic Markers</td>
<td>• Prognostic Markers</td>
<td>• Prognostic Markers</td>
<td>• Prognostic Markers</td>
</tr>
<tr>
<td>• Patient Preference</td>
<td>• Patient Preference</td>
<td>• Patient Preference</td>
<td>• Patient Preference</td>
</tr>
</tbody>
</table>

**Standard front-line:**
- Cytarabine-based therapies
- Auto SCT in 1st Remission
- Maintenance Rituximab

**Intensive approach:**
- Cytarabine-based
- Auto SCT in 1st remission
- Maintenance Rituximab

**Less-Intensive approach:**
- Bendamustine-based
- R-CHOP-based
- ? Maintenance Rituximab

**Standard:**
- Bendamustine-based
- R-CHOP
- ? Maintenance Rituximab

**Consider:**
- R-Lenalidomide

**No Standard Approach:**
- R-Lenalidomide (if feasible)
- R-monotherapy
- ?Ibrutinib (not indicated)
- Supportive care
Front-line considerations

• Observation should be considered in all asymptomatic patients regardless of age

• Ibrutinib / Acalabrutinib not indicated in the front-line alone or combination
  • Consider in frail patients who cannot tolerate chemotherapy

• Clinical trial enrollment preferred in all settings
Identification of Patients with Indolent MCL

- Patients with indolent MCL can potentially be observed.

Martin et al, J Clin Oncol 2009

Cohen et al, Cancer 2016

Calzada et al, Leuk Lymphoma 2018
Consistent Predictors of Deferred Therapy

- Lack of B-symptoms
- Normal LDH
- Leukemic, non-nodal presentation (i.e., CLL-like)
- Good ECOG Performance Status
- Ki67 < 30%
- Lack of blastoid variant

*NOTE:* MIPI risk score has not been associated with selection of deferred therapy.

# Outcomes of Deferred Therapy

<table>
<thead>
<tr>
<th>Series</th>
<th>Number of Deferred Patients (%)</th>
<th>Median time to treatment (Range)</th>
<th>Median OS (Deferred Pts)</th>
<th>Median OS (Immediate Pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin 2009 (Cornell)</td>
<td>31 / 97 (32)</td>
<td>12 months (4-128)</td>
<td>Not Reached (4.6 years)</td>
<td>5.3 years</td>
</tr>
<tr>
<td>Abrisqueta 2017 (B.C.)</td>
<td>74 / 439 (17)</td>
<td>35.5 months (5-79)</td>
<td>5.5 years</td>
<td>4.2 years</td>
</tr>
<tr>
<td>Cohen 2016 (NCDB)</td>
<td>492 / 8029 (6)</td>
<td>4 months (3-38)*</td>
<td>6.6 years</td>
<td>-</td>
</tr>
<tr>
<td>Kumar 2015 (MSKCC)</td>
<td>91 / 404 (23)</td>
<td>23 months</td>
<td>10.6 years</td>
<td>9.4 years</td>
</tr>
<tr>
<td>Calzada 2016 (Multicenter)</td>
<td>72 / 395 (18)</td>
<td>7.8 months (3-121)*</td>
<td>11.8 years</td>
<td>11.6 years</td>
</tr>
</tbody>
</table>

*Converted from days as reported in reference

- All retrospective projects – No randomized studies
- Successful identification of low risk patients
Front-line Options (Intensive)

- **R-CHOP/R-DHAP (MCL Younger)**

- **R-MaxiCHOP / R-AraC (Nordic)**


Other front-line approaches

• R-DHAP (Lyma)
• R-HyperCVAD (+/- SCT)
  • 2 year PFS (w/ SCT): 82%
  • Challenges with collection
  • Toxic in patients > 60
  • 15-year FFS (w/o SCT): 30% in patients < 65 years
• R-BAC
• BR/R-AraC

Role of ASCT in 1\textsuperscript{st} Remission

- Use based on older study with CHOP (+/- R)

Dreyling, \textit{Blood}, 2005
EA4151: MRD-based assessment of SCT

Step 0
- Any induction regimen
- Enroll before, during, or after induction

Submit diagnostic tissue for molecular testing

Clonal Marker Present?
Yes
Post-induction restaging + Submission of blood for MRD assessment
MRD-neg CR

MRD-neg PR or MRD indeterminate

No
No informative marker: MRD indeterminate

Step 1
Stratify:
- MIPI-c
- Intensive vs non-intensive

Randomization

Arm A
ASCT + Rituximab x 3 years

Arm B
Rituximab x 3 years

Arm C
ASCT + Rituximab x 3 years

Arm D
ASCT + Rituximab x 3 years

* Rituximab maintenance is every 8 weeks x 3 years starting 60-120d post Auto-HCT
EA4181: Randomized phase 2 trial < 70

- Alternating R-bendamustine/R-Cytarabine (2 g/m2)
- Alternating R-bendamustine/R-Cytarabine (2 g/m2) + Acalabrutinib
- R-bendmustine + Acalabrutinib

MRD -/+ CR/PR
Triangle Study

R

R-CHOP/ R-DHAP x 6

ASCT

Observation

A + I:

R-CHOP/ R-DHAP x 6 + Ibrutinib

ASCT

2 yrs Ibrutinib maintenance

Observation

I:

R-CHOP/ R-DHAP x 6 + Ibrutinib

2 yrs Ibrutinib maintenance

Observation
Non-intensive Approaches

- Bendamustine-Rituximab
- R-Lenalidomide

Rituximab Maintenance

• LyMa trial: R-DHAP x 4 \(\rightarrow\) ASCT
  • Patients randomized to rituximab maintenance x 3 years vs observation
  • 4-year PFS 83% vs 64%, \(p< 0.001\)

• Non-transplant setting
  • Benefit after R-CHOP (MCL Older)
  • Unclear benefit after B-R

Le Gouill et al, NEJM 2017; Kluin-Nelemans ASH 2017; Rummel ASCO 2017
Summary

- Mantle cell lymphoma is heterogeneous and management is based on disease biology, patient fitness, comorbidities, and other factors.

- Upfront approaches range from observation to intensive therapy w/ ASCT

- Trials pending may markedly alter our approach to treatment by addressing:
  - Role of ASCT
  - Minimal Residual Disease
  - Role of novel therapies including ibrutinib
THANK YOU!
Question 1

• A 50 year old male with newly diagnosed mantle cell lymphoma presents for initial evaluation. He is feeling well with no symptoms. He was diagnosed with MCL based on a mild lymphocytosis that was identified during a routine physician visit. He is otherwise healthy.
• A PET/CT shows some scattered adenopathy measuring between 1.5 and 2.5 cm.
• Bone marrow biopsy is positive for MCL with a Ki67 of 20%

How would you approach this patient?
1) Initiate cytarabine-based therapy followed by auto transplant
2) Initiate treatment with R-Bendamustine
3) **Observe with close follow-up**
4) Initiate treatment with ibrutinib
Question 2

• The 50 year old male in question 1 was observed for 18 months but ultimately developed symptomatic disease and received R-DHAP x 4 followed by consolidation with stem cell transplant. He is in complete remission and has recovered from the transplantation.

What do you recommend to improve his overall survival?

1) No further therapy is indicated – initiate observation protocol

2) Rituximab maintenance

3) Ibrutinib maintenance

4) Lenalidomide maintenance