Management of MCL

Current standards and future studies

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Mantle cell lymphoma

- clinical variation
- chemotherapy standards (first line)
- targeted approaches
Mantle cell lymphoma Histology

A classical; B small cell; C pleomorphic; D: blastoid; E: classical & pleomorphic; F: classical/pleomorphic

Tiemann, Brit J Haematol 2005
RB signal pathway in MCL I

cdk4/cyclin D1

RB

RB P
Risk factor proliferation: MCL 35

Scott, JCO 2017
Combined MIPI-c
Overall survival

Patients >65 years

Patients <65 years

Hoster, JCO 2016
MCL: a spectrum of disease

„indolent“ MCL (15%)  „classical“ MCL (80%)  „transformed“ (5%)
MCL: two kind of diseases

WHO classification 2017
Mantle cell lymphoma

- molecular pathogenesis
- chemotherapy standards (first line)
- targeted approaches
Multicenter Evaluation of MCL
Annecy Criteria fulfilled

event free interval after chemotherapy in stages III + IV

Dreyling, ASCO 1999
<table>
<thead>
<tr>
<th>young patient (&lt;65)</th>
<th>elderly patient (&gt;65)</th>
<th>compromised patient</th>
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| **First line treatment** | **conventional immuno-chemotherapy** (e.g. R-CHOP, VR-CAP, BR) | **Best supportive care?**  
R-Chlorambucil  
BR (dose-reduced) R-CVP |
| dose-intensified immuno-chemotherapy (e.g. R-CHOP, high dose Ara-C)  
⇒ Autologous SCT  
⇒ Rituximab maintenance | conventional immuno-chemotherapy (e.g. R-CHOP, VR-CAP, BR)  
⇒ Rituximab maintenance | |
| **1. relapse** | | |
| immuno-chemotherapy (e.g. R-BAC, BR)  
or targeted approaches  
**discuss:**  
- allogeneic SCT | immuno-chemotherapy (e.g. BR, R-BAC)  
or targeted approaches  
**discuss:**  
- Rituximab maintenance  
- radioimmunotherapy | Immuno-chemotherapy (e.g. BR)  
or targeted approaches |
| **higher relapse** | | |
| Targeted approaches: Ibrutinib, Lenalidomide, Temsirolimus, Bortezomib (preferable in combination)  
Alternatively: repeat previous therapy (long remissions) | | |
Immuno-chemotherapy in MCL
Progression-free survival

Rummel, Lancet 2013
Optimal treatment for elderly MCL?

Induction

Immuno-chemotherapy!

=> lymphoma remission

Consolidation

maintenance

+/- SCT

=> MRD elimination
**MCL elderly**

**Survival rates (R-CHOP)**

**Remission duration**
- Median follow-up: 4.6 years
- R, median = 5.8 years
- IFN, median = 1.9 years
- no, median = 0.8 years
- p < 0.0001

**Overall survival**
- Median follow-up: 38 months
- R, median not reached
- IFN, median = 64 months
- p = 0.0061

Kluin-Nelemans, NEJM 2012
### First line treatment

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**Rituximab maintenance** | **Best supportive care?**  
R-Chlorambucil  
BR (dose-reduced)  
R-CVP |

### 1. relapse

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**discuss:**  
- **Rituximab maintenance**  
- **radioimmunotherapy** | **Immuno-chemotherapy** (e.g. BR)  
or targeted approaches |

### Higher relapse

- Targeted approaches: Ibrutinib, Lenalidomide, Temsirolimus, Bortezomib (preferable in combination)  
Alternatively: repeat previous therapy (long remissions)
European MCL Network

patients <65 years

3 x R-CHOP

3 x R-CHOP

DexaBEAM (stem cell mobilization)

Cyclo 120 mg/kg + TBI 12 Gy

PBSCT

PR, CR!

3 x R-CHOP
3 x R-DHAP alternating

(stem cell mobilization after course 4)

PR, CR!

TBI 10 Gy
Ara-C 4 x 1.5 g/m²
Melphalan 140 mg/m²

PBSCT

Hermine, Lancet 2016
MRD at end of induction
Effect of ASCT

Hermine, Lancet 2016
**MCL younger**

**Time to treatment failure**

- **TTF - primary analysis**

- **median follow-up = 5.3**
  - R-DHAP, median = 7.3
  - R-CHOP, median = 3.9
  - $p = 0.0382$

### Numbers At Risk

<table>
<thead>
<tr>
<th></th>
<th>Years</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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</thead>
<tbody>
<tr>
<td>R-DHAP</td>
<td></td>
<td>232</td>
<td>190</td>
<td>170</td>
<td>150</td>
<td>111</td>
<td>77</td>
<td>52</td>
<td>26</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>R-CHOP</td>
<td></td>
<td>234</td>
<td>176</td>
<td>153</td>
<td>125</td>
<td>82</td>
<td>53</td>
<td>35</td>
<td>24</td>
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_Hermine, Lancet 2016_
R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or oxaliplatin or carboplatin)

R-BEAM: Rituximab 500mg/m2 d-8; BCNU 300mg/m2 d-7; Etoposide 400mg/m2/d d-6 to -3; aracytine 400mg/m2/d d-6 to d-3; melphalan 140mg/m2 d-2

Le Gouill, NEJM 2017
Survival rates from Randomization

Le Gouill, NEJM 2017
### First line treatment

**young patient (≤65)**
- dose-intensified immuno-chemotherapy (e.g. R-CHOP, high dose Ara-C)
  - Autologous SCT
  - Rituximab maintenance

**elderly patient (>65)**
- conventional immuno-chemotherapy (e.g. R-CHOP, VR-CAP, BR)
  - Rituximab maintenance

**compromised patient**
- Best supportive care?
  - R-Chlorambucil BR (dose-reduced) R-CVP

### 1. relapse

**immuno-chemotherapy (e.g. R-BAC, BR) or targeted approaches**
- discuss:
  - allogeneic SCT

**immuno-chemotherapy (e.g. BR, R-BAC) or targeted approaches**
- discuss:
  - Rituximab maintenance
  - radioimmunotherapy

**Immuno-chemotherapy (e.g. BR) or targeted approaches**

### higher relapse

Targeted approaches: Ibrutinib, Lenalidomide, Temsirolimus, Bortezomib (preferable in combination)
Alternatively: repeat previous therapy (long remissions)

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*Dreyling, ESMO CR MCL 2017*
Targeted strategies in MCL

Proteasome inhibition
- R-CHOP +/− Bortezomib

mTOR inhibition
- BeRT
  - BR-Temsirolimus
- T3 protocol chemotherapy + Temsirolimus
- MCL 3001
  - Ibrutinib vs Temsirolimus

Immune modulation
- NLG-MCL4
  - BR-Lenalidomide
- R2-B
  - BR-Lenalidomide
- SPRINT
  - Lenalidomide vs investigator’s choice
VR-CAP vs R-CHOP: Progression-free survival

- Median follow-up 40 months; 298 (61%) PFS events
- 59% improvement with VR-CAP vs R-CHOP (hypothesized: 40% improvement)
- Median PFS by investigator was 16.1 vs 30.7 months with R-CHOP vs VR-CAP; 307 (63%) events; HR 0.51, p<0.001; 96% improvement with VR-CAP

Presented by: Franco Cavalli, MD
Targeted strategies in MCL

- **Proteasome inhibition**
  - R-CHOP+/-Bortezomib

- **mTOR inhibition**
  - BeRT
    - BR-Temsirolimus
  - T3 protocol
    - chemotherapy+
      - Temsirolimus
  - MCL 3001
    - Ibrutinib vs Temsirolimus

- **Immune modulation**
  - NLG-MCL4
    - BR-Lenalidomide
  - R2-B
    - BR-Lenalidomide

- **Targeted strategies in MCL**
  - SPRINT
    - Lenalidomide vs investigator’s choice
mTOR Inhibitor Temsirolimus

Rini, Clin Cancer Res 2008
**BeRT**: Benda/Rituximab/Temsirolimus

- **Bendamustin**: 90 mg/m²
- **Rituximab**: 375 mg/m²
- **Temsirolimus**: 25/50/75 mg

- **D1**: Be Be
- **D8**: R
- **D15**: T T
- **D22**: T
- **D29**: T

Hess, Leukemia 2015
**Rel. Mantle cell lymphoma**

**Lenalidomide**

Median PFS, mo (95% CI)
- Lenalidomide: 8.7 (5.5-12.1)
- IC: 5.2 (3.6-6.9)

HR (95% CI)
- Lenalidomide: 0.61 (0.44-0.84); P = 0.004

*Trneny, Lancet Oncol 2016*
Mantle cell lymphoma (first line) 
Rituximab-Lenalidomide

Ruan, NEJM 2015
European MCL Network
MCL R2 elderly

1st line induction:
- 8x R-CHOP
- 6x R-CHOP/Ara-C

PR/CR ~80%

Rituximab maintenance + Lenalidomide
15 mg daily d1-21, q28 days

Treatment: max. 2 years

sponsor: LYSARC
central pathology: W. Klapper
MRD diagnostics: M. Ladetto, C. Pott, MH Delfau
Mantle cell lymphoma

B-cell receptor pathway
BTK inhibitor Ibrutinib

Adverse events (>15%)
Ibrutinib in RR MCL: bleeding events
Patients with previously treated MCL

Randomize

1:1 → Stratified by number of prior lines of therapy and by sMIPI

**Ibrutinib (N = 139)**
- Oral ibrutinib 560 mg daily starting Cycle 1, Day 1
- Treat to PD or unacceptable toxicity

**Temsiorlimus (N = 141)**
- Intravenous temsirolimus 175 mg on Cycle 1, Days 1, 8, 15; then 75 mg on Days 1, 8, 15 of all subsequent cycles
- Treat to PD or unacceptable toxicity

Crossover to ibrutinib (after IRC-confirmed PD; n = 32)

Dreyling, Lancet 2015
Progression-free survival

At a 2-year landmark, the PFS rate was 41% for ibrutinib versus 7% for temsirolimus.

Investigator-assessed HR for ibrutinib versus temsirolimus was 0.43 (95% CI, 0.32-0.58)

Dreyling, Lancet 2015
Relapsed mantle cell lymphoma
Failure under ibrutinib

Peter, Blood 2016
Ibrutinib-Lenalidomide-R
Survival rates and p53 status

NORDIC MCL6 PHILEMON

- TP53 mut (n=11)
- no TP53 mut (n=38)

p=0.43

NORDIC MCL2/3

- no TP53 mut (n=136)
- TP53 mut (n=15)

p<0.0001

Eskelund, ASH 2016
Background: Mechanism of action of Venetoclax

1. An Increase in BCL-2 Expression Allows the Cancer Cell to Survive
   - Pro-apoptotic Proteins (BAX, BAK)
   - Anti-apoptotic Proteins (BCL-2)

2. Venetoclax Binds to and Inhibits Overexpressed BCL-2
   - BH3-only
   - Mitochondria

3. Apoptosis is Initiated
   - Apoptosome
   - Active Caspase
   - APAF-1
   - Cytochrome C
   - Procaspase
Objective responses

Davids, JCO 2017
AIM Study: Marrow Flow MRD Kinetics*

Study Timepoint

- Ibrutinib Wk 1 onwards
- Venetoclax Wk 5 onwards

BM Involvement and MRD: Change during Initial Therapy

- Complete Response
- Partial Response
- Progressive Disease

Flow MRD-neg 10 of 13 (77%) assessable CR
AIM: Progression Free & Overall Survival

Progression Free Survival

Overall Survival

Median Follow-up 8.3 months (1.4 to 17.7+ months)

OS 81% at 1 year (95%CI: 66–100)
PFS 74% at 1 year (95%CI: 58–94)

TAM, ICML 2017
European MCL Network
Study generation 2017

< 65 years

MCL younger:
R-CHOP/DHAP => ASCT
R-CHOP/DHAP + I => ASCT => I
R-CHOP/DHAP + I => I

> 60 years

MCL elderly R2:
R-CHOP vs R-CHOP/Ara-C
=> Rituximab M
+/- Lenalidomide

> 65 years

MCL elderly I:
BR +/− Ibrutinib
=> Rituximab M
+/- Ibrutinib

1. Relapse

R-HAD +/- Bortezomib

2. Relapse (or not qualifying for R-HAD)

Ibrutinib vs Temsirolimus

BeRT
BR-Temsirolimus
First line MCL
Suggested therapeutic algorithm

TP53, NOTCH1, other → Mutational screening → SOX11 negative without adverse mutations

MIPI-c risk

high
- HD AraC + anthracyclin + biological agent

high intermediate
- HD AraC + biological agent

low intermediate
- HD AraC +
  - MRD+
  - MRD-

low
- conventional treatment
  - (low tumor load: watch & wait)

ASCT

Post-treatment risk evaluation: MRD

- MRD+
  - consolidation/maintenance

- MRD-
  - observation

Dreyling, Haematologica 2016
annual meeting 2017 in Chur