MANTLE CELL LYMPHOMA

Dr Tobias Weiglein, MD, MHBA & Prof Dr Martin Dreyling, MD
Ludwigs-Maximilians University Munich, Medical Department for Hemathology and Oncology, Campus Großhadern, Munich, Germany
1. To understand the biology of MCL
2. To understand the diagnostic and prognostic factors in MCL
3. To choose the most appropriate first line treatment for different subsets of patients
4. To know about molecular targeted substances and therapy concepts at relapse and refractory disease
MANTLE CELL LYMPHOMA

Epidemiology and characteristics

- Accounts for approximately 6% of all NHL cases
- Median age 60-70 years
- Male predominance (men > women 3:1)
- Very frequent extranodal disease manifestation
- Since its worldwide recognition in 1994, it has been known to have a dismal prognosis ("the worst lymphoma to have"), with a median overall survival (OS) rate of 3 years only
PROGNOSIS OF MANTLE CELL LYMPHOMA
PROGNOSIS OF MCL

Overall survival of MCL compared to other B-NHL entities

MANTLE CELL LYMPHOMA
HISTOLOGY

A classical; B small cell; C pleomorphic; D: blastoid; E: classical & pleomorphic; F: classical/pleomorphic
MANTLE CELL LYMPHOMA BIOLOGY

RB signal pathway in MCL I

cdk4/ cyclin D1

RB

RB P
MANTLE CELL LYMPHOMA: A SPECTRUM OF DISEASE

“Indolent” MCL (15%)

“Classical” MCL (80%)

“Transformed” (5%)

Naive B cell → Early MCL → Classical MCL → Blastoid MCL

Germline
ATM
CHK2

\[ t(11;14) \]
Cyclin D1

RB1
p27

ATM
CHK2

Complex karyotypes

INK4A/CDK4/RB1
ARF/MDM2/p53

High proliferation

Figure 9: Tumor neoplastic cells are positive for cyclin D1 and located in the mantle zone of lymphoid follicle. At the upper and lower sides of the right side, primary follicles show numerous neoplastic cells (immunoperoxidase, anti-cyclin D1, ×100).

Dreyling M, ASCO Educational 2014. Courtesy of Prof Martin Dreyling
PROGNOSIS OF MCL

- In 1980-1990s overall median survival (OS) was dismal with 2-4 years at time of diagnosis

- Prognosis depending on clinical variables
  - Age
  - Stage
  - Performance Score
  - LDH

- And biological features
  - Proliferation Index (Ki67)
  - growth pattern (blastoid vs. classical)

PROGNOSIS OF MCL

Risk factor proliferation: MCL 35

Scott DW, J Clin Oncol, 35(15) 2017: 1668–77. Reprinted with permission. © 2017 American Society of Clinical Oncology. All rights reserved.
MIPI and MIPI-c

**MIPI:**
- Age
- ECOG Performance status
- LDH level
- WBC count

**MIPI-c:**
- MIPI + Ki-67 index

The more refined combined MIPI (MIPI-c) classifies MCL patients into four prognostic groups dependent on MIPI group and Ki-67 index.

According to MIPI-c, patients are assigned to the low, low-intermediate, high-intermediate, or high risk group.

PROGNOSIS OF MCL

Combined MIPI (MIPI-c)

Patients >65 years

Patients <65 years

Numbers At Risk

years from registration

MANTLE CELL LYMPHOMA TREATMENT
MANTLE CELL LYMPHOMA TREATMENT

Optimal treatment for MCL?

Induction

Immuno-chemotherapy!

=> lymphoma remission

Consolidation

Maintenance

+/- SCT

=> MRD elimination
MANTLE CELL LYMPHOMA TREATMENT

Young, fit patients

**First Line Therapy***

*Watch and Wait Strategy in Indolent, Low Tumour Burden Patients Possible

**Young Fit Patient (<65)**
- Organ Function: ↑↑
- Comorbidity: ↓↓
- Performance Status: ↑↑

Intensive Therapy:
- Long Term Survival

**Old Fit Patient (>65)**
- Organ Function: ↑↓
- Comorbidity: ↓↓
- Performance Status: ↑↓

Less Intensive Therapy:
- Remission and Better Survival

**Old Unfit Patient (>65)**
- Organ Function: ↓↓
- Comorbidity: ↑↑
- Performance Status: ↓↓

Mild Supportive Therapy:
- Symptom Control, Survival

**Dose-intensified Immunochemotherapy**
- R-CHOP / R-DHAP followed by Autologous SCT
- + R- Maintenance

**Conventional Immunochemotherapy**
- e.g. R-CHOP, B-R
- VR -CAP
- + Rituximab Maintenance

**Mild Therapy**
- e.g. R-Chlorambucil
- B-R
- R-CVP
- Best Supportive Care?
MANTLE CELL LYMPHOMA TREATMENT

Role of anti-CD-20 antibody rituximab

- Adding rituximab to CHOP clearly improves PFS an ORR, (ORR 94% vs. 75%, CR 34% vs. 7%)
- Improvement of ORR and PFS with addition of rituximab to polychemotherapy have been confirmed in successive trials
- R-Chemo standard of care in first and successive treatment lines

MANTLE CELL LYMPHOMA TREATMENT

Why CHOP?

MANTLE CELL LYMPHOMA TREATMENT

Autologous SCT and IFN survival rates

Remission duration

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p</th>
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<tr>
<td>R</td>
<td>0.60</td>
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Overall survival

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Presented at ASH Annual Meeting 2008 Courtesy of Prof Martin Dreyling.

MANTLE CELL LYMPHOMA TREATMENT
Young fit patients <65 years

3 x R-CHOP

3 x R-CHOP

DexaBEAM (stem cell mobilisation)

Cyclo 120 mg/kg + TBI 12 Gy

PBSCT

PR, CR!

PR, CR!

3 x R-CHOP

3 x R-DHAP

alternating

(stem cell mobilisation after course 4)

TBI 10 Gy

Ara-C 4 x 1.5 g/m²

Melphalan 140 mg/m²

PBSCT

MANTLE CELL LYMPHOMA TREATMENT

Time to treatment failure in “MCL younger” trial

From The Lancet, 388(10044), Hermine O, et al. (Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network, 388:565–75. Copyright © 2016 with permission from Elsevier.)

Parameters:
- Median follow-up = 5.3 years
- R-DHAP, median = 7.3 years
- R-CHOP, median = 3.9 years
- p = 0.0382

Numbers At Risk:
- R-DHAP: 232, 190, 170, 150, 111, 77, 52, 26, 6, 0
- R-CHOP: 234, 176, 153, 125, 82, 53, 35, 24, 6, 0

Graph shows the survival probabilities over time for R-DHAP and R-CHOP treatments.
MANTLE CELL LYMPHOMA TREATMENT

MRD at end of induction: Effect of ASCT

MANTLE CELL LYMPHOMA TREATMENT

Post ASCT rituximab maintenance: “LyMa” trial

**R-DHAP**: Rituximab 375 mg/m²; aracytine 2 g/m² x2 IV 3 hours injection 12 hours interval; dexamethasone 40 mg d1-4; Cisplatin 100 mg/m² d1 (or oxaliplatin or carboplatin)

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

MANTLE CELL LYMPHOMA TREATMENT

Post ASCT rituximab maintenance: “LyMa” trial

MANTLE CELL LYMPHOMA TREATMENT

First line treatment young patients: Conclusion

Watch and wait strategy in indolent, low tumour burden patients possible

Rituximab – chemo is standard of care in any induction therapy

Induction-regimes containing high-dose cytarabin seem to further improve PFS, OS and MRD negativity. ORR is 80-90% with 40-50% CR

High-dose chemotherapy, followed by autologous stem cell transplantation prolongs PFS and OS and is the current standard of care for younger patients, generally providing high responses and long survival rates, but is hampered by acute and long-term toxicity

R-hyper-CVAD or R-HD-MTX-Ara-C regimen, followed by a consolidation with BEAM and ASCT is an alternative dose intensified (and toxic) approach and are debated, especially between European and American clinical groups

Rituximab maintenance every 2 months for 3 years after ASTC improves OS
# Mantle Cell Lymphoma Treatment

## Older Patients / Unfit Patients

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### First Line Therapy

- **Intensive Therapy:** Long Term Survival
- **Less Intensive Therapy:** Remission and Better Survival
- **Mild Supportive Therapy:** Symptom Control, Survival

### Dose-intensified Immunochemotherapy
- R-CHOP / R-DHAP followed by Autologous SCT
- + R-Maintenance

### Conventional Immunochemotherapy
- e.g. R-CHOP, B-R
- VR -CAP
- + Rituximab Maintenance

### Mild Therapy
- e.g. R-Chlorambucil
- B-R
- R-CVP
- Best Supportive Care?

*Watch and Wait Strategy in Indolent, Low Tumour Burden Patients Possible*
Bendamustine in combination with rituximab can be applied with comparable ORR and OS rates as R-CHOP, but with lesser side effects.
MANTLE CELL LYMPHOMA TREATMENT

MCL elderly survival rates (R-CHOP)

- Rituximab as maintenance therapy every two months following R-CHOP chemotherapy significantly improves PFS

BORTEZOMIB IN MCL

VR-CAP vs. R-CHOP

- No maintenance Therapy after induction!
- 59% improvement with VR-CAP vs. R-CHOP (hypothesised: 40% improvement)
- Median PFS by investigator was 16.1 vs. 30.7 months with R-CHOP vs. VR-CAP

Conclusion

In elderly patients with compromised organ function and performance score, conventional immuno-chemotherapy is the first choice with ORR of ~90%

Fludarabin-containing regimens are inferior to R-CHOP in terms of OS

Rituximab as maintenance therapy every two months following R-CHOP chemotherapy significantly improves PFS

Bendamustin in combination with Rituximab can be applied with comparable ORR and OS rates as R-CHOP, but with lesser side effects

Bortezomib in combination with R-CAP (VR-CAP) shows better PFS compared to R-CHOP with more (haemoto-) toxicity and may be a good option for aggressive (e.g. blastoid) MCL in elderly patients not eligible for ASCT

In very frail patients Rituximab mono or Rituximab and oral Chlorambucil is an effective and well tolerated regime, especially in low risk or rather indolent cases
MANTLE CELL LYMPHOMA TREATMENT

First Relapse / Refractory Disease

Young Fit Patient (<65)
- Organ Function ↑↑
- Comorbidity ↓↓
- Performance Status ↑↑

Old Fit Patient (>65)
- Organ Function ↓↓
- Comorbidity ↑↑
- Performance Status ↓↓

Old Unfit Patient (>65)
- Organ Function ↓↓
- Comorbidity ↑↑
- Performance Status ↓↓

Immunochemotherapy
- e.g. B-R, R-BAC
- Repeat First Line?
- Consider: Allogeneic SCT

Targeted Approaches
- Repeat First Line?
- Consider: R- Maintenance
- Radioimmunotherapy

Higher Relapse

Targeted Approaches: Ibrutinib, Lenalidomide, Temsirolimus, Bortezomib (preferable in combination with chemotherapy)
- Alternatively: repeat previous therapy (long remissions)

R, Rituximab, B-R, Bendamustine-Rituximab, R-CHOP, Rituximab/ Cyclophosphamide/ Doxorubicin/ Vincristine/ Prednisone,
VR-CAP, Bortezomib/Rituximab/Cyclophosphamide/Doxorubicin/Prednisone
R-DHAP, Dexamethason/high-dose Cytarabine/Cisplatin, R-CVP- Rituximab/Cyclophosphamide/Prednison
R-BAC, Rituximab/Bendamustine/Cytarabine, SCT- Stem-Cell Transplantation
TARGETED SUBSTANCES AT RELAPSE

Temsilimus is registered in EU and has shown superiority over other agents in heavily pre-treated patients with ORR of 23%, and PFS of 4.8 months.

Patients with relapsed or refractory mantle cell lymphoma ineligible for intensive chemotherapy or stem-cell transplantation have longer progression-free survival with lenalidomide compared to investigator's choice of monotherapy.

TARGETED SUBSTANCES AT RELAPSE
Ibrutinib

Patients with previously treated MCL

RANDOMIZE

Ibrutinib (N = 139)
Oral ibrutinib 560 mg daily starting Cycle 1, Day 1

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

Temsirilimus (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

Treat to PD or unacceptable toxicity

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

Reprinted from *The Lancet*, 387(10020), Dreyling M, *et al.* Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study, 770–8, Copyright 2015, with permission from Elsevier.
TARGETED SUBSTANCES AT RELAPSE

Adverse events ibrutinib

*AEs were updated with an estimated median follow-up of 26.7 months
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First line MCL suggested therapeutic algorithm

- **Mutational screening**
  - **MIPI-c risk**
    - **High**
      - HD AraC + anthracyclin + biological agent
    - **High intermediate**
      - HD AraC + biological agent
    - **Low intermediate**
      - HD AraC
    - **Low**
      - Conventional treatment (low tumour load: watch and wait)
    - **SOX11 negative without adverse mutations**
- **ASCT**
- **Post-treatment risk evaluation: MRD**
  - **MRD+**
    - Consolidation/maintenance
  - **MRD-**
    - Observation

Conclusion I

Immuno-chemotherapy is standard of care at relapse and is chosen depending on patient fitness and age, comorbidities, earlier therapy and duration of response.

The mTOR-inhibitor temsirolimus can achieve better ORR, PFS and OS compared to mono-chemotherapy at relapsed or refractory disease.

In relapsed or refractory disease ibrutinib increases ORR from 40% to 72% and PFS (hazard ratio 0.43; median 8.4 months) compared to temsirolimus. OS is not affected by ibrutinib (due to crossover).

Lenalidomide also increases ORR and PFS compared to physicians choice in relapsed and refractory disease.
THERAPY AT RELAPSE

Conclusion II

Bortezomib also shows promising activity in MCL as monotherapy or in combination, yet no Phase III data is available in refractory or relapsed disease, e.g. a combination of bortezomib and bendamustin + rituximab (BERT) shows high activity in a Phase II study.

Rituximab maintenance therapy after salvage immunochemotherapy leads to improved PFS and can be discussed.

If HD-Ctx and ASCT has not been performed as first line therapy, eligible patients should be offered a HD-Ctx and ASCT after lymphoma remission in relapse.

Young fit patients relapsing after HD-Ctx and ASCT should be offered an allogenic transplantation if a donor is available.
OUTLOOK: BCL-2 INHIBITION

Venetoclax

OUTLOOK: CHEMOTHERAPY FREE COMBINATIONS?

First line: Rituximab-lenalidomide

OUTLOOK: COMBINATION THERAPY
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
THANK YOU!