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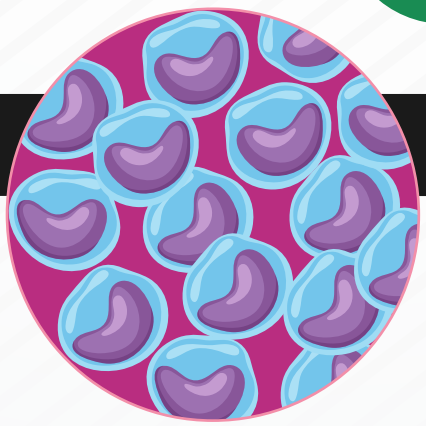
Mantle Cell Lymphoma — Clinical Evaluation, Diagnosis, and Novel Treatments

Highlights from the ASH Congress on 'Mantle Cell, Follicular, and Other Indolent B Cell Lymphomas' held from December 6th to 15th 2023



Treatment Approaches for Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a rare and aggressive type of malignant blood cancer[1]

- Comprises approximately 6% of all non-Hodgkin lymphomas
- Poor prognosis compared to other types of lymphomas
- High relapse rates

Although considered incurable, available treatments offer ways of extending survival in patients

Conventional treatment[1]

- Chemoimmunotherapy
- New therapeutic drugs
  - Bruton's tyrosine kinase (BTK) inhibitors (BTKi)
  - Chimeric antigen receptor T-cells (CAR-T)
  - Immunomodulatory drugs like lenalidomide
- Stem cell transplant

Assessing the response to treatment in MCL necessitates a sensitive tool to notice small changes in amount of disease

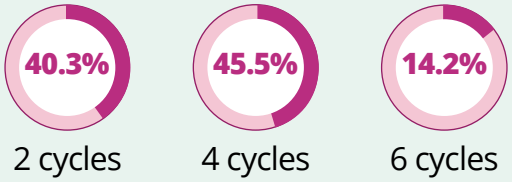
Minimal residual disease (MRD)[2]

MRD refers to the extent of tumor cells persisting in a patient's blood or bone marrow after treatment

- Testing negative for MRD suggests:
  - Undetectably low tumor cell count
  - Deep remission

Predictability and timing of MRD[2]

Percentage of patients with MCL who tested negative for MRD after:



MRD offers the best predictive ability for prognosis after 4 cycles of treatment

Next generation sequencing (NGS) and MRD[3]

Peripheral blood (PB) MRD data obtained using NGS after two cycles of non-intensive chemoimmunotherapy predicts:

- Remission duration (p = 0.133)
- Need for maintenance therapy

Prognostic factor and treatment strategies for MCL

Rare immunotype variant characterized by the overexpression of B-cell lymphoma 6 (BCL6), termed as BCL6+MCL

Prognostic value of BCL6 and clinical outcomes[4]

Mata-analysis involving 537 patients

The positivity rate of B-cell lymphoma 6 (BCL6) in the cells of MCL patients is:

- Inversely linked to overall survival
- Positive correlation to the expression of prognostic indicators CD10 and SOX11

Prognostic scoring systems provide information about the prognostic categorization, management, classification, and future tailored treatment of MCL variants

Prognostic value of progression-free survival at 24 months (POD24)[5]

Early progression of disease within two years, POD24, is considered a potential indicator of OS

Cohort study
1,386 MCL patients

Non-POD24
981

POD24
299

POD24 is a surrogate for overall survival in MCL

Prognostic value of TP53 mutation[6]

TP53 mutations, occurring in 10–20% of MCL patients, show heterogeneous clinical impact

Expression of TP53 is linked to poor prognosis

Clinical trials for MCL treatment

Phase 2 trial of Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) for TP53-mutant MCL[7]

Multicenter, investigator-initiated phase 2 trial

25 patients

Median follow-up 16.1 months

Outpatient regimen of BOVen

- Well-tolerated by patients
- High response rates
- Linked to high rates of undetectable MRD

CDC20: A new therapeutic target[8]

- Overexpression of cell division cycle 20 (CDC20 homologue) is associated with prediction of disease progression in MCL patients
- CDC20 expression is higher in MCL cells compared to healthy cells
- CDC20 is a viable therapeutic target for MCL drugs

Progress in treatment outcomes and age[9,10]

Treatment outcomes have improved for MCL patients in the last two decades, with the advent of new frontline drugs	Improvements are limited in patients aged ≥ 80	Improvements in treatment outcomes can be attributed, in part, to BTKi therapy	Significant enhancements in progression-free survival (PFS) and overall response rates (ORR)

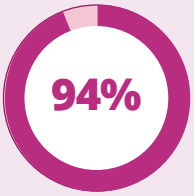
Treatment for older MCL patients[11]

Older MCL patients have poor tolerance for intense chemotherapy or radiotherapy

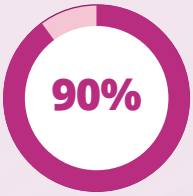
Poor prognosis

Phase 2 trials of a chemotherapy-free treatment strategy involving acalabrutinib with rituximab (AR)

Best response observed at a median of 12 cycles



Overall response rate



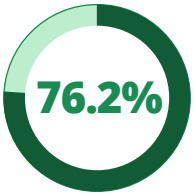
Complete responses

Prospective phase 2 study for MCL treatment strategies

Phase 2 trials of orelabrutinib, lenalidomide, rituximab (OLR)[12]

6 cycles of induction therapy

Overall response rate



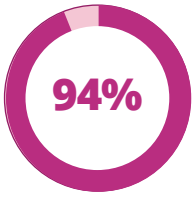
Complete responses

- Manageable toxicity
- Synergistic antitumor activity observed in OLR therapy

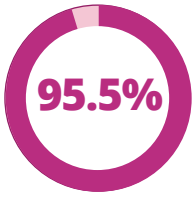
Trials involving rituximab[13,14]

Phase 2 trial involving rituximab, chemotherapy, and acalabrutinib followed by stem cell transplantation

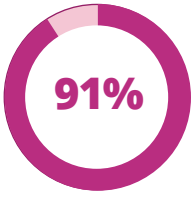
Median follow up 11.8 months



12-month PFS



Overall Survival



Complete responses

Compared to rituximab-based therapies, obinutuzumab-based therapies showed

Higher PFS	Comparable toxicity	Higher OS

Predicting early relapse in MCL[15]

Novel prognostic model index developed through machine learning algorithm can

- Predict early progression of disease
- Identify high-risk patients

Novel treatments for relapsed/refractory MCL

Chemoimmunotherapy

- Acalabrutinib, venetoclax, and obinutuzumab (AVO) - phase 1[16]

Monotherapy

- Pirtobrutinib monotherapy - phase 1/2[17]
- Novel BTKi called LP-168 - phase 1[18]

Phase 3 trial for assessing monotherapy using Glofitamab is underway[19]

CAR-T cell therapy for relapsed/refractory MCL

Chimeric antigen receptor T (CAR-T) cell therapy is a groundbreaking treatment for relapsed/refractory MCL

Successful new trials

- Phase 1 trial of CAR-T cell-based drug called 'IM19'[20]
- Phase 2 trial of CAR-T cell-based relmacabtagene autoleucel 'relma-cel'[21]
- Real world study of brexucabtagene autoleucel or 'brexu-cel'[22]

Effect of race and ethnicity on clinical outcomes with MCL[23]

Compared to their White counterparts, MCL patients who are Black, have following showed:

- Earlier MCL diagnosis
- Worse overall survival rates

MCL is not the leading cause of death in patients who have attained 24-month event-free survival (EFS24) through first line immunotherapy[24]

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