touch HAEMATOLOGY

Managing the practicalities of CAR T-cell therapies in patients with R/R MCL:

Current considerations and future strategies

Practice aid for relapsed or refractory mantle cell lymphoma

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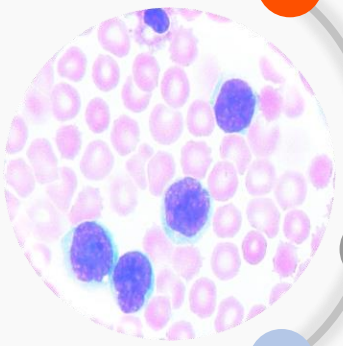
MCL: Overview[1]



1

DISEASE CHARACTERISTICS

- Clinically and biologically heterogeneous
- The genetic hallmark of the disease is the presence of t(11:14)

2

RISK STRATIFICATION

- Several clinical and biological features are predictive of survival outcomes in frontline and R/R settings

3

BIOLOGY

- Comprehensive biological characterization leads to optimal disease risk stratification

4

GENETICS

- The single strongest negative prognostic marker is the presence of a *TP53* mutation

Tools for risk stratification following diagnosis[1]

Tool	Overview	Risk score: Low; intermediate; high
MIPI	• Weighted summation of pre-treatment values of: Age; ECOG PS; LDH; WCC	<5.70; 5.70–6.19; ≥6.20
S-MIPI	• Simplified for clinical use • A sum of scores based on: Age; ECOG PS; LDH; WCC	0–3; 4–5; 6–11
MIPI-b	• Combined biological score: MIPI + weighted Ki67%	<5.7; 5.7–6.5; ≥6.5
MIPI-c	• MIPI risk combined with Ki67% (<30% or ≥30%)	MIPI-low, Ki67 <30%; MIPI-high, Ki67 ≥30% Two intermediate (low vs high) categories are derived from different combinations of MIPI risk and Ki67%

- Risk stratification is critical at time of diagnosis
- MIPI-c provides robust and reproducible prognostic scoring in the immunotherapy era

NCCN 2023 guidelines: Therapeutic regimens for R/R MCL[2]

Second and subsequent lines of therapy

Preferred regimens

- Covalent BTKi (continuous)*
  - Acalabrutinib
  - Zanubrutinib
- Lenalidomide + rituximab

Other recommended

- Covalent BTKi (continuous)
  - Ibrutinib† ± rituximab

Third and subsequent lines of therapy

- Non-covalent BTKi
  - Pirtobrutinib‡
- Anti-CD19 CAR T-cell therapy
  - Brexucabtagene autoleucel§

*Acalabrutinib and zanubrutinib have not been shown to be effective for ibrutinib-refractory MCL with *BTK* C481S mutations. Patients with ibrutinib intolerance have been successfully treated with acalabrutinib or zanubrutinib without recurrence of symptoms. †Head-to-head clinical trials in other B-cell malignancies have demonstrated a more favourable toxicity profile for acalabrutinib and zanubrutinib compared with ibrutinib without compromising efficacy. ‡Pirtobrutinib inhibits both wild-type and C481S mutant BTK and has been shown to be effective in patients with intolerance or disease that is refractory to prior covalent BTKis without recurrence of prior symptoms. Pirtobrutinib may be used to treat patients with disease progression or intolerance to covalent BTKi therapy. §Only given after chemoimmunotherapy and BTKi.

Patient selection for CAR T-cell therapy

MCL DISEASE CHARACTERISTICS[3–5]

- Progression on ≥2 lines of therapy
- MIPI: high risk
- *TP53* mutation
- Blastoid morphology

PATIENT CHARACTERISTICS[3,4]

- Favourable ECOG PS
- No severe organ dysfunction
- No active CNS involvement
- No acute uncontrolled infections

EXTRA PRECAUTIONS REQUIRED[4]

- High disease burden
- Active infections
- Low platelet count
- High serum LDH

Bridging therapy prior to CAR T-cell therapy[4]

- **Goal**: Prevent disease progression; debulk tumours
- **Choice**: Depends on patient (disease burden; prior therapies; comorbidities), HCP preference and time to CAR T-cell infusion

Chemotherapy

- Inhibits tumour cell proliferation
- May transiently reduce disease burden

Immunotherapy

- mAbs: Immune effectors (NK cells, macrophages) recruited to kill tumour cells
- BsAbs: Effector T cells recruited to tumour site

Radiotherapy

- Immunogenic debulking strategy
- Delivered focally

Management of toxicities associated with CAR T-cell therapy[6,7]

- Patient monitoring before, during and after CAR T-cell therapy is critical for early recognition of potential toxicities and timely intervention
- CAR T-cell-related toxicities can generally be reversed though the use of appropriate management strategies

Toxicity	Symptoms	Management
CRS	• Fever • Gastrointestinal (nausea, vomiting, diarrhoea) • Hypotension • Tachycardia • Hypoxia • Chills	**Early symptoms** • Monitor and support with antipyretics/analgesics as needed • Exclude infection **According to grade and patient need** • Tocilizumab or anti-IL-6 therapy • Corticosteroids (if no improvement in 12–24 hours)
Cytopenias	• Abnormal blood counts • Increased infections[8] • Bleeding complications (thrombocytopenia)[8]	**Rule out myelodyplastic syndrome** • Transfusion • Growth factor support
HLH/MAS	• Fever • Rapidly rising and high ferritin (>5000 ng/mL) • Elevated serum bilirubin/AST/ALT/CRP • Haemophagocytosis in bone marrow or organs	**Treat as per CRS** • Anti-IL-6 therapy, e.g. tocilizumab • Corticosteroids
Hypogammaglobulinaemia	• B-cell aplasia • Low antibody levels • Increased risk of infection	• IVIG infusion until serum IgG normalizes in patients experiencing frequent or severe infections

Management of toxicities associated with CAR T-cell therapy[6,7]

Toxicity	Symptoms	Management
Infections	**Various, for example:** • CDI: Diarrhoea (primary symptom; other symptoms vary with disease severity)[9] • URTI: Sore throat, blocked nose, fever, muscle aches[10] • PJP: Fever, dry cough, breathing difficulties[11]	• Infection prevention and prophylaxis (no consensus on strategies to use[12]) • Target source of infection
Neurological	**Heterogeneous, including**: • Encephalopathy • Delirium • Aphasia • Lethargy	• Corticosteroids

Abbreviations

ALT, alanine transaminase; AST, aspartate aminotransferase; -b, biologic; BsAb, bispecific antibody; BTKi, Bruton tyrosine kinase inhibitor; -c, combined; CAR, chimeric antigen receptor; CD, cluster of differentiation; CDI, *Clostridioides difficile* infection; CNS, central nervous system; CRP, C-reactive protein; CRS, cytokine release syndrome; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCP, healthcare provider; HLH/MAS, haemophagocytic lymphohistiocytosis/macrophage activation syndrome; Ig, immunoglobulin; IL, interleukin; IVIG, intravenous Ig; LDH, lactate dehydrogenase; mAb, monoclonal antibody; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; NCCN; National Comprehensive Cancer Network; NK, natural killer; PJP, *Pneumocystis jirovecii* pneumonia; R/R, relapsed or refractory; S-, simplified; URTI, upper respiratory tract infection; WCC, white cell count.

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