ASSOCIATION OF CANCER CARE CENTERS

TREATMENT FOR RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

BACKGROUND

Mantle cell lymphoma (MCL) accounts for approximately

5% **of all non-Hodgkin lymphoma (NHL) cases in the United States and Europe.[1]**

MCL is historically considered an incurable disease with a median progression-free survival as long as 5 years, but late relapses still occur.[1] Because MCL is rare, only highly specialized providers will see large numbers of patients with relapsed or refractory (R/R) disease. This creates a challenge for providers to stay informed on recent clinical evidence supporting treatment selection and use of novel targeted therapies. In response to this need, the Association of Cancer Care Centers (ACCC) has developed this tip sheet to provide a snapshot of the latest information in treatment for patients with MCL, with a focus on new treatment options for patients with R/R disease.

CLINICAL PRESENTATION

Many patients present with palpable lymphadenopathy and systemic symptoms at the time of diagnosis and are found to have stage 3 or 4 disease with bone marrow involvement. A smaller subset of patients may present with peripheral lymphocytosis without symptoms, which is associated with a better prognosis.[2] The diagnosis is made by analysis of the morphology, immunophenotype, and molecular genetic features of the malignant cells, usually obtained from lymph nodes, blood, or bone marrow. The typical immunophenotype is CD5+, CD20+, CD23-, CD200-, and FMC7+. Nearly all cases (except rare ones) express cyclin D1, a key feature of the diagnosis.[1] A high ki-67 proliferation index and TP53 mutation are associated with significantly worse outcomes and poor response to conventional therapy.[2] With each subsequent relapse, prognosis tends to worsen.[1]

INITIAL TREATMENT

Decision on initial treatment should be made using a risk-stratified approach, incorporating MCL international prognostic index (MIPI) score, which accounts for age, performance status, lactic acid dehydrogenase (LDH), and white blood count (WBC) count. Low MIPI scores, typically those with indolent MCL, may be considered for close observation without active treatment.[1] Patients with a TP53 mutation should be considered for referral to a clinical trial due to association with significantly worse prognosis and historically poor response to conventional therapy. In general, initial treatment involves chemo-immunotherapy and consideration of autologous stem cell treatment if complete remission is achieved and dependent on performance status. Multiple chemotherapy regimens exist with little randomized data to prove superiority of one combination over another. Maintenance therapy includes use of rituximab, with or without ibrutinib.[3] However, a full description of initial treatment options is beyond the scope of this review.

RELAPSED/REFRACTORY TREATMENT

Following initial therapy, patients should be monitored with history and physical and labs every 3-6 months for 5 years and annually thereafter. Surveillance CT for chest/abdomen/pelvis (C/A/P) should be considered every 6-12 months for up to 2 years after treatment, and then annually.[1] When relapse is identified, patients should undergo another workup including biopsy and full restaging to determine the best options based on the updated risk profile.[4] Refractory disease is determined by clear progression on imaging or repeat biopsy if imaging is not conclusive.[1]

The median age at diagnosis for MCL is 67 years, and there is a relatively strong male predominance.[1]

TREATMENT OPTIONS FOR REFRACTORY/RELAPSED MANTLE CELL LYMPHOMA

Chemoimmunotherapy

Chemotherapy regimens often in combination with rituximab

- Historical treatment for patients with R/R MCL until new agents were introduced[3]
- Only with agents the patient had not used in previous lines of therapy

Covalent Bruton Tyrosine Kinase (BTK) Inhibitors

Ibrutinib, acalabrutinib and zanubrutinib[6,7]

- Preferred agents for second-line therapy after initial chemoimmunotherapy
- Tend to be well tolerated and side effects can be managed with dose reductions
- Median Progression Free Survival (PFS) in the studies of these drugs ranges from 12 to 33 months
- Adverse reactions to monitor include gastrointestinal and hematologic toxicities, hypertension, atrial fibrillation or flutter, in addition to infections and hemorrhage. If the patient is at risk of cardiac toxicity or bleeding, consider second generation BTK inhibitors
- Dose adjustments are necessary when patients take concomitant CYP3A4 inhibitors or inducers
- Secondary primary malignancies have been seen, with the most common being skin cancers. Advise patients to use sun protection and monitor patients closely

Lenalidomide + Rituximab[5]

- Approved for R/R patients after two prior therapies, one of which must have included bortezomib
- Overall response rate 26%, median duration of response was 16.6 months

Non-Covalent BTK Inhibitors

Pirtobrutinib[8]

- Highly specific BTK inhibitor that has shown benefit in patients who are refractory to covalent BTK inhibitors. Approved January 2023 for patients with MCL after at least 2 lines of therapy, including a covalent BTK inhibitor
- Efficacy outcomes included an overall response rate of 58%, complete response rate of 20%, and median duration of response of 22 months
- Associated with lower rates of grade ≥3 hypertension, hemorrhage, and atrial fibrillation or flutter compared with earlier generation covalent BTK inhibitors

CAR T-cell Therapy

Brexucabtagene autoleucel[9]

- Overall response rate was 91%, complete response rate 68%, median duration of response 28 months, median progression-free survival 26 months
- Due to the complex logistical challenges and close monitoring requirements for frequent, serious adverse reactions, such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS), CAR T-cell therapies must be administered at a REMS certified health care facility
- Consider in patients who have failed prior chemotherapy and covalent BTK inhibitor therapy[10]
- Exclusion criteria include patients with active or serious infection, prior stem cell transplant, history of central nervous system disorders, or evidence of brain metastases[9]

FUTURE THERAPIES

Clinical trials are ongoing to develop novel therapies for the treatment of R/R MCL. Some of the more advanced trials with potential treatments on the horizon include:

Additional BTKs

Nemtabrutinib, vecabrutinib, fenebrutinib[11]

- ➜ Only nemtabrutinib has an ongoing trial enrolling patients with B-cell malignancies

CD20 Targeting Bispecific Antibodies

Epcoritamab, glofitamab[13]

- ➜ Well tolerated in trials, overall response rate 50-83%[14]

BCL-2 Inhibitor

Venetoclax[12]

- ➜ Currently under investigation as monotherapy and in combination regimens for the management of R/R MCL
- ➜ May be of use in patients with high-risk features such as Ki-67 >30% and TP53 mutation

BEST PRACTICES

Optimal treatment is based on many factors including disease aggressiveness, performance status, age, and MIPI scores. All treatment decisions should be made with shared decision-making, taking into consideration patient preferences.

Preferred second-line therapy is a covalent BTK inhibitor in most patients.

Prescribers must ensure their patients understand the side effects that are common with MCL therapies.

Patients should be closely followed and assessed to ensure proper management of commonly encountered adverse events. This will optimize adherence and help prevent premature treatment failure and suboptimal outcomes.

Community prescribers are highly encouraged to collaborate with larger academic centers to enhance patient access to the more logistically complex therapies, such as CAR T-cell therapy, stem cell transplantation, or clinical trials.

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A publication from the ACCC education program, "Evolving Treatment Landscape for Relapsed/Refractory Mantle Cell Lymphoma." Learn more at **accc-cancer.org/MCL.**

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