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Updates in the Treatment of Mantle Cell Lymphoma: A Canadian Expert Framework

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Introduction

Mantle cell lymphoma (MCL) is a B cell Non-Hodgkin Lymphoma that develops in the mantle zone of the lymph node. It is more common in men and is usually diagnosed at an advanced stage with involvement of lymph nodes, bone marrow, and potentially the gastrointestinal tract.¹ MCL accounts for 5-10% of all new NHL cases per year in Canada, which is estimated at 11,400 for 2022.² While most patients respond to initial treatment, relapses occur early and MCL generally shows a variable response to subsequent treatments, often with limited duration of benefit.³

Two main subtypes of MCL can be distinguished that arise from in situ MCL lesions. The most common subtype, classic MCL, arises from these cells with limited or no immunoglobulin heavy chain variable region (IGHV) mutations. Cells from this subtype express SOX11, are genetically unstable, and have

naïve B cell-like characteristics. Classic MCL is more often nodal and extranodal and may eventually progress to aggressive blastoid or pleomorphic MCL. The other subtype, leukemic non-nodal MCL, arises from cells that have undergone IGHV somatic hypermutations, do not express SOX11, and exhibit characteristics of memory B cells. This subtype can have an indolent clinical behavior for a long time, often several years, but frequently acquires *TP53* and other mutations and progresses to a more aggressive subtype.^{1,2}

Treatment options have expanded significantly over the past decades, with improvements in both overall survival (OS) and progression-free survival (PFS) compared to earlier treatment eras.^{4,5} This Canadian expert framework aims to discuss the management considerations for patients with MCL, and will present both front-line treatment options as well as those for relapsed and refractory disease.

Methods

- Relevant literature for this framework was selected by the authors.
- Therapies were selected based on availability/approval in Canada.
- Included studies were Phase I, II, or III trials, both single-arm and randomized.
- Where available, pooled analyses and long-term follow-up study updates were included.
- Prospective and retrospective cohort studies, as well as case reports and expert opinions, were evaluated.

Front-Line Therapy

Treatment choices for front-line therapy of MCL are primarily based on patients' characteristics such as age and fitness, as well as disease biology (**Figure 1**). For a subset of patients at any age, observation (known as a 'watch and wait' strategy) can be a reasonable option. Patients suitable for observation include those with a low tumor burden, leukemic non-nodal presentation, non-bulky disease, and absence of disease-related symptoms including B symptoms. Most of these patients can be observed for over 12 months and studies have shown a longer OS for this patient group compared with patients who are treated within this timeframe⁶, suggesting observation in this patient group is not detrimental to their overall outcomes. However, most patients on a watch and wait strategy will eventually develop progressive MCL and require front-line therapy.

Young Patients

Young and fit patients for whom observation is not recommended should be considered for intensive therapies. Most of such intensive therapies involve induction chemotherapy with rituximab, followed by high-dose (HD) chemotherapy and autologous stem cell transplant (auto-SCT), with or without subsequent maintenance with rituximab. Auto-SCT has been shown to improve progression-free survival (PFS), especially when performed during the first complete response (CR).⁷ Multiple strategies are available for induction immunochemotherapy prior to HD chemotherapy and auto-SCT. The European MCL Network Younger trial compared R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by total body irradiation-based conditioning and auto-SCT vs. R-CHOP alternating with R-DHAP (rituximab, dexamethasone, HD cytarabine, and cisplatin) followed by conditioning using HD cytarabine and auto-SCT. The alternating chemotherapy approach resulted in a longer time to treatment failure and improved OS, even though this treatment resulted in increased grade 3-4 toxicities.^{8,9} Maintenance rituximab (MR) was not a standard therapy when this study was conducted.

Long-term follow-up data from the Nordic MCL2 trial, which treated patients with maxi-CHOP, rituximab, and HD cytarabine before BEAM (bis-chloroethylnitrosourea, etoposide, cytarabine, melphalan) or BEAC (bis-chloroethylnitrosourea, etoposide, cytarabine, cyclophosphamide) as HD regimens before auto-SCT, showed a median OS of 12.7 years and a median PFS of 8.5 years. Therefore, long response durations can be achieved in a moderate proportion of patients with intensive, cytarabine-based strategies.¹⁰

R-DHAP followed by auto-SCT and MR in younger patients is also associated with favorable outcomes, with a 4-year event-free survival (EFS) of 79%, and OS of 89%.¹¹ Additionally, hyperfractionated intense-dose cyclophosphamide, vincristine, continuous intravenous (i.v.) doxorubicin, and dexamethasone (Hyper-CVAD) is another option for cytoreduction before auto-SCT.¹² The addition of rituximab to hyper-CVAD has an objective response rate (ORR) of 97% with a CR rate of 87%. This strategy results in a 3-year failure-free survival (FFS) for patients ≤65 years of 73% (vs. 64% for the total population). The toxicity of this strategy is significant and is not recommended for older patients.^{13,14}

Bendamustine-based regimens are increasingly being used prior to auto-SCT. The S1106 study compared induction rituximab plus hyper-CVAD against rituximab plus bendamustine (BR) and

showed similar efficacy after five years of follow-up. However, rituximab plus hyper-CVAD resulted in increased grade 3-4 toxicities and inadequate stem cell mobilization, leading to early study termination.¹⁵ Induction regimens combining bendamustine and cytarabine (plus rituximab) prior to auto-SCT are also effective.¹⁶

A direct comparison between BR in a real-world cohort from British Columbia and the R-CHOP/R-DHAP arm of the MCL Younger trial suggested similar response rates, outcomes, and proportion of patients moving to auto-SCT.¹⁷ Ultimately, different rituximab-containing regimens can be used prior to auto-SCT, and there is no single standard of care regimen. MR after auto-SCT improves outcomes in younger patients as shown in the LYMA trial. Patients receiving 3 years of MR had a 5-year PFS of 66.7% and OS of 83.5%, compared with a 5-year PFS of 21.5% and OS of 55.1% for those not on MR. MR has also been shown to be associated with favorable outcomes post auto-SCT in real-world cohorts.^{11,18}

Key Takeaways:

- ✓ **Observation can be considered in asymptomatic patients with leukemic non-nodal MCL, low tumor burden, and non-bulky disease.**
- ✓ **Young and fit patients should receive induction chemotherapy with rituximab, followed by HD chemotherapy and auto-SCT.**
- ✓ **Maintenance rituximab should be considered in responding patients after auto-SCT.**

Elderly Patients

Older and frail patients might not be able to tolerate the intensive strategies recommended for younger patients. There is no formal age cut-off, although most prospective studies have used 65 years of age to distinguish between young and elderly. Age is a continuous variable, and a subgroup of fit patients >65 years of age (typically 66-70 years) could be reasonably treated with an intensive strategy. The European MCL Network Elderly trial randomized transplant-ineligible patients to R-CHOP vs. R-FC (rituximab, fludarabine, cyclophosphamide) induction, followed by a second randomization to rituximab or IFN- α maintenance. In this study, R-FC resulted in shorter OS and higher mortality rates during the first remission, but more importantly, R-CHOP with MR was associated with improved OS.^{19,20}

R-CHOP in which vincristine is replaced with bortezomib (VR-CAP) was shown to improve response rates, response duration, PFS, and OS over R-CHOP in patients ineligible for auto-SCT.^{21,22} Treatment benefit was most pronounced in patients with low or intermediate-risk disease.²³ However, VR-CAP increases the risk of neutropenia and thrombocytopenia,²¹ and given this higher rate of toxicity as well as the cost of bortezomib, its widespread adoption in older patients has been limited.

In this patient group, randomized and retrospective data suggest BR is associated with a more favorable toxicity profile and improved outcomes compared to R-CHOP.^{5,24,25}

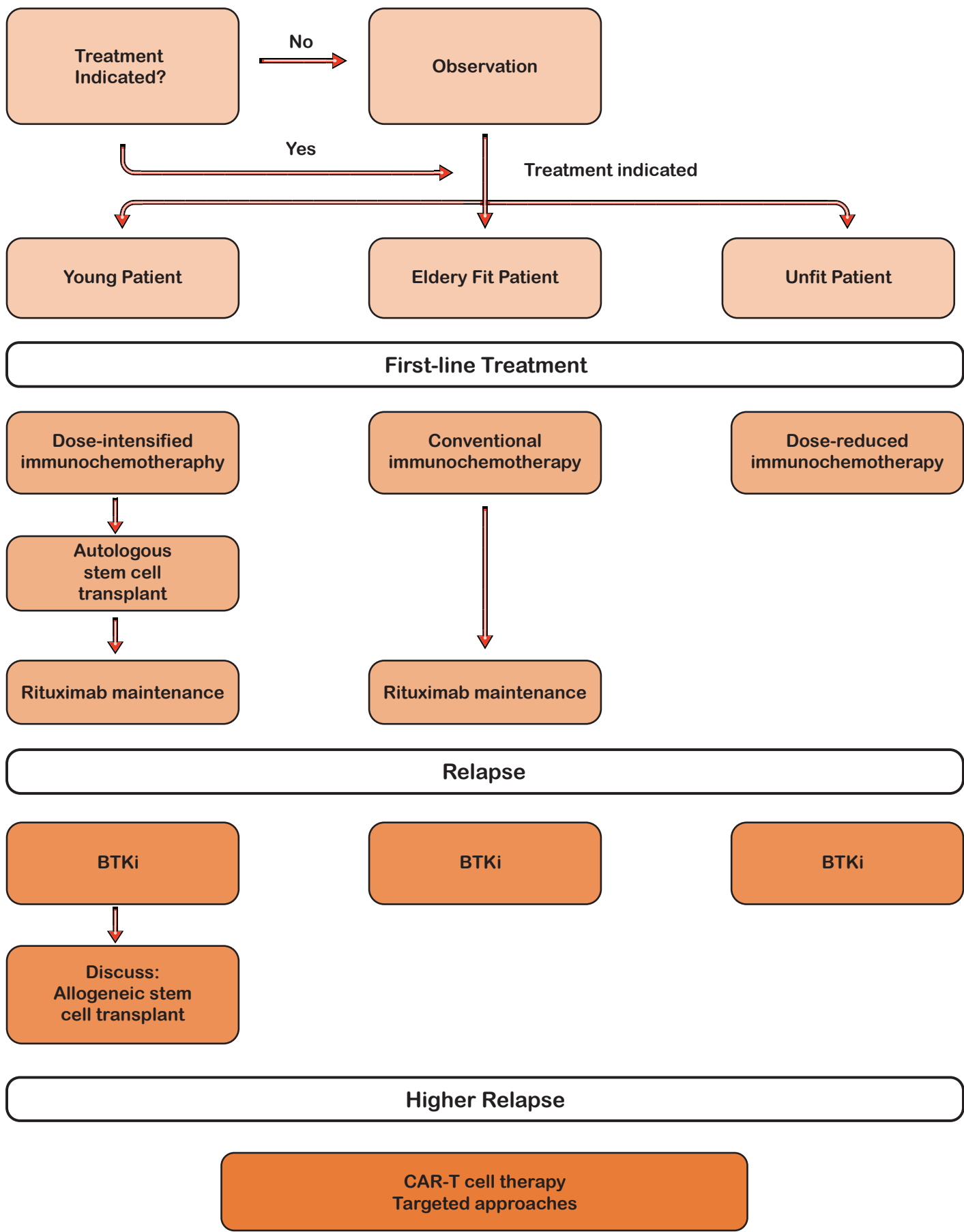


Figure 1: Flow chart depicting therapy recommendations for patients with mantle cell lymphoma at various stages of disease. BTKi: Bruton Tyrosine Kinase inhibitor; CAR: chimeric antigen receptor.

	Dosing	ORR/CR	Median DOR	Survival	Grade ≥ 3 AEs	Refs
BTK inhibitors						
Ibrutinib	560 mg/day	68-77%/ 19-27%	17.5-23.1 mo.	Median PFS 12.5-15.6 mo. Median OS 26.7-30.3 mo.	Neutropenia (13-17%), thrombocytopenia (9-12%), pneumonia (12.7%), anemia (8-10%), major bleeding (10%), atrial fibrillation (4-6%), diarrhea (3-6%), fatigue (4-5%), dyspnea (5%), abdominal pain (5%), hypertension (5.1%), peripheral edema (2%), decreased appetite (2%), rash (2%), pyrexia (1%)	Wang 2013 (N=115; Phase II, single-arm), Rule 2019 (N=370; pooled analysis 2x Phase II, 1x Phase III), Dreyling 2016 (N=280; Phase III RCT)
Zanubrutinib	160 mg twice daily 320 mg once daily	84-85% /25-78%	18.5-24.9/ not reached at 35.3 mo.	Median PFS 21.1-25.8 mo. Median OS 38.2 mo	Anemia (6-13%), infections (19%), pneumonia (9-13%), myalgia (9%), neutropenia (9-19%), major bleeding (5-9%), lymphopenia (7%), thrombocytopenia (6-7%), peripheral edema (6%), TLS (6%), atrial fibrillation (1-3%), hypertension (3-12%), diarrhea (3%), fatigue (3%), back pain (3%), SPM (3%)	Tam, 2021 (N=32; Phase I/II single-arm) Zhou 2021 (N=112; pooled analysis of 2x Phase I/II, single-arm) Song 2022 (N=86; Phase II, single-arm)
Acalabrutinib	100 mg/twice daily	81%/40%	Not reached	Median EFS 67%. Median OS 87%.	Neutropenia (11%), anemia (9%) pneumonia (5%), diarrhea (3%), headache (2%), fatigue (1%), myalgia (1%), nausea (1%) bleeding (1%),	Wang 2018 (N=124; Phase II, single-arm)
BCL-2 inhibitors						
Venetoclax	800 mg/day*	75%/21%	-	Est. median PFS 14 mo. Est. 1-yr OS 82%	*Anemia (15%), neutropenia (11%), thrombocytopenia (9%), TLS (18%), fatigue (7%), diarrhea (3%), constipation (2%)	Dauids 2017 (N=28, Phase I, single-arm) Dauids 2018 (update)
Ibrutinib + venetoclax	560mg+ 400mg*/daily	/67-71%	Not reached	-	TLS (8%), neutropenia (33%), thrombocytopenia (17%), anemia (12%), diarrhea (12%), infection (8%), atrial fibrillation (8%)	Tam 2018 (n=24; Phase II single-arm)
CAR-T cell therapy						
KTE-X19	2x10 ⁶ CAR-T cells/kg bodyweight	91%/68%	28.2 mo.	Median PFS 25.8 mo. Median OS 46.6 mo.	Neutropenia (85%), thrombocytopenia (51%), anemia (50%), NE (31%), hypotension (22%), hypophosphatemia (22%), hypoxemia (21%), encephalopathy (19%), CRS (15%), pyrexia (13%), hyponatremia (10%), alanine aminotransferase (8%), hypokalemia (7%)	Wang 2022 (N=68; Phase II, single-arm)
Proteasome Inhibitor						
Bortezomib	1.3 mg/m ² days 1,4,8,11 of a 3-week cycle	29-50%/5-21%	9.2-10 mo.	Median PFS 6.7 mo. Median OS 23.5-61.1 mo.	**Thrombocytopenia (11-43%), lymphopenia (34%), fatigue (4-31%), infection (3-20%), dyspnea (5%), anemia (16%), neutropenia (10%), neurologic toxicity (5-13%), myalgia (5-10%), diarrhea (3-7%), nausea/vomiting (3-6%), liver toxicity (4%), anorexia (3%), rash (2-3%), constipation (3%), dizziness (3%), musculoskeletal pain (2%)	Strauss 2006 (N=24, Phase III single-arm), Fisher 2006 (N=155, Phase II single-arm), O'Connor 2005 (N=11, Phase II single-arm), Goy 2009 (N=155, Phase II single-arm), Belch 2007 (N=29, Phase II, single-arm)
Bortezomib + rituximab	1.5 mg/m ² days 1,4,8,11 of a 3-week cycle + 375 mg/m ² on days 1 and 8	29%/29%		Est. 2-yr PFS 24%	**Neurotoxicity (52%), fatigue (36%), neutropenia (20%), thrombocytopenia (20%), diarrhea (12%), constipation (12%), anemia (8%), anorexia (4%), nausea/vomiting (4%), rash (4%), febrile neutropenia (4%), myositis (4%)	Biacocchi 2011 (N=14, Phase II, single-arm)
Bortezomib + gemcitabine	1.0 mg/m ² on days 1,4,8,11/3 weeks + 1000 mg/m ² on days 1, 8	60%/11.5%		Median PFS 11.4 mo.	Granulocytopenia (48%), thrombocytopenia (40%), pain (15%), fatigue (11%), headache (8%), cough (8%), hypertension (4%), dehydration (4%), infection (8%), muscle weakness (4%), neuropathy (4%), neuropathic pain (4%), dyspnea (8%), hypoxia (4%), pleural effusion (4%)	Kouroukis 2011 (N=26, Phase II, single-arm)
Bortezomib + bendamustine + rituximab	1.3 mg/m ² days 1,4,8,11 + 90 mg/m ² days 1, 4 + 375 mg/m ² day 1/ every 4 weeks	71%		** 2-year PFS 47%	**thrombocytopenia (17%), neutropenia (17%), febrile neutropenia (6%), peripheral neuropathy (6%), fatigue (6%), hypotension (6%), infection (6%), nausea (3%), constipation (3%), diarrhea (3%), back pain (3%)	Friedberg 2011 (N=7, Phase II single-arm)
IMiD						
Lenalidomide	25 mg/daily	28-40%/5-7.5%	16.1-16.6 mo.	Median PFS 4.0-8.7 mo. Median OS 19.0-27.9 mo.	Neutropenia (43-44%), thrombocytopenia (18-27%), anemia (8-11%), leukopenia (6-8%), febrile neutropenia (6%), diarrhea (4-6%), pneumonia (4-8%), dyspnea (5%), pyrexia (0-3%), fatigue (1-7%), constipation (0-1%), asthenia (1%), anorexia (1%)	Trneny 2016 (N=170, Phase II, randomised) Goy 2013 (N=134, Phase II, single-arm)
Allogeneic SCT		95%/48-90%		Median EFS 18 mo. Median OS 27 mo.	Acute GVHD (10-26%), chronic GVHD (17-61%)	Cook 2010 (N=70, retrospective), LeGouill 2012 (N=70, retrospective),

Table 1. Summary of different classes of agents for MCL by dosing, response rates, survival benefit and AE profile

*Stepwise increased.

**Based on study in several lymphoma subtypes. AE: adverse events; BCL-2: B cell lymphoma 2; BTK: Bruton tyrosine kinase; CR: complete response; CRS: cytokine release syndrome; DOR: duration of response; EFS: event-free survival; GVHD: graft-versus-host disease; mg: milligram; Mo: months; NE: neurologic events; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial; SCT: stem cell transplant; SPM: second primary malignancy; TLS: tumor lysis syndrome.

Additionally, in a small phase II study the immunomodulatory imide drug (IMiD) lenalidomide combined with rituximab was associated with an ORR of 92% and those responding to treatment had an improvement in quality of life. However, this strategy has a high rate of grade 3 and 4 AEs and is not broadly available in Canada for patients with MCL.²⁶ While long-term MR following R-CHOP was shown to reduce the risk of progression or death compared to IFN- α maintenance in the European MCL Elderly trial^{19,20} in a subgroup study of the MAINTAIN trial, MR was not associated with improved PFS after BR.²⁷ However, this study was underpowered, and large real-world cohorts have shown improved OS for MR after BR.²⁸

In patients responding to induction immunochemotherapy, maintenance with lenalidomide and rituximab (R2M) has demonstrated a PFS improvement over MR alone, resulting in a 2-year PFS of 76.6% vs. 60.8% for MR. However, AEs were more abundant in the R2M group, and dose reductions for lenalidomide were necessary in 46% of patients.²⁹ It is unclear whether this study will influence clinical practice, especially in light of the recent phase III SHINE trial, which showed that combining ibrutinib with BR and MR improved PFS (median 80.6 months) compared to chemoimmunotherapy (median PFS 52.9 months), with a higher CR rate and similar AE rates and quality of life outcomes.³⁰ Other trials are currently investigating BR plus acalabrutinib (NCT02972840) or zanubrutinib plus rituximab in this setting (NCT04002297). These new data and agents are of interest for this patient population, but it currently remains unclear how these may impact the Canadian treatment landscape over time.

Key Takeaways:

- ✓ **For elderly patients who are unfit for intensive therapy, BR followed by MR is associated with excellent outcomes.**
- ✓ **VR-CAP is associated with improved OS compared to R-CHOP in this population, although it is associated with increased toxicity and cost, and has not been compared against BR.**
- ✓ **Phase II data support R2 in elderly patients, although there are toxicity and cost considerations, and the performance of this regimen against BR or R-CHOP has not been evaluated in a randomized setting.**
- ✓ **Ibrutinib in combination with BR and MR was associated with improved PFS over BR and MR alone in the SHINE trial.**

Relapsed/Refractory (R/R) MCL

Even though initial response rates to front-line therapies are high in many patients with MCL, the majority will eventually experience disease relapse. Additionally, a subgroup of patients will develop disease refractory to front-line treatments. There are several standard and emerging therapies in R/R MCL (**Figure 1, Table 1**).

Bruton Tyrosine Kinase Inhibitors (BTKi)

Covalent BTKi are currently the most common therapy in R/R MCL.³¹ The activity of ibrutinib, a first-generation BTKi, was initially established in a phase II study in patients with heavily pre-treated MCL; the ORR was 68% with a CR rate of 21%. Previous bortezomib treatment did not affect the response rate. The estimated median DOR and PFS were 17.5 and 13.9 months, respectively.³² Most adverse events (AEs) were mild or moderate, and grade ≥ 3 AEs were predominantly hematological.

Also in a randomized setting, ibrutinib demonstrated an improved median PFS of 14.6 months vs. 6.2 months for temsirolimus. The ORR to ibrutinib was 72% with a CR of 19%, while temsirolimus resulted in an ORR of 40% and a CR of 1%. Ibrutinib was better tolerated than temsirolimus with 68% grade ≥ 3 AEs vs. 87% for temsirolimus. The most common AEs for both drugs were thrombocytopenia, anemia, neutropenia, diarrhea, and fatigue.³³

A long-term follow-up pooled analysis of single agent ibrutinib from three clinical trials confirms that responses to ibrutinib develop over time, but more importantly, this analysis suggests that outcomes are more favorable when ibrutinib is used early in the course of R/R MCL.^{34,35}

Two highly selective, second-generation BTKi, zanubrutinib and acalabrutinib, have also been evaluated in R/R MCL in prospective phase I/II trials.

Zanubrutinib was assessed in a recent phase II study in 86 patients with a follow-up of 35.3 months there were no cases of atrial fibrillation and only 9.3% of discontinuations were due to AEs. This study showed an ORR for young patients of 90.6%, and a CR of 82.8% while patients aged 65 and older had both an ORR and CR of 63.6%. Zanubrutinib was shown to have a 3-year PFS of 48% and a 3-year OS of 75%.³⁶

Acalabrutinib was assessed in a phase II trial of patients who had received a median of two previous treatments. At a median follow-up of 15.2 months, results demonstrated an ORR of 81% with 40% of patients experiencing a CR. The median DOR was 13.8 months, and the 12-month median DOR was 72%. The most common AEs were grade 1-2, and the most common grade ≥ 3 were neutropenia and pneumonia. Treatment was discontinued in 44% of subjects, of which 7% were due to AEs and 31% were due to progressive disease.³⁷

Therefore, the main consideration for choice between the three covalent BTKi is their toxicity profile. In a randomized clinical trial in Waldenström macroglobulinemia in which zanubrutinib and ibrutinib were directly compared, AEs, including atrial fibrillation, diarrhea, bleedings, and other AEs that might lead to treatment discontinuation were less common in the zanubrutinib-treated group.³⁸ Furthermore, a randomized study in chronic lymphocytic leukemia (CLL) showed that acalabrutinib caused significantly less atrial fibrillation, infections, and other AEs causing discontinuation than ibrutinib.³⁹

Real-world utilization has shown primary and acquired resistance to ibrutinib is common.⁴⁰ A retrospective study assessing disease progression of patients on ibrutinib did not identify subsequent treatments that improved outcomes post-ibrutinib failure, suggesting that after development of ibrutinib resistance patients have limited treatment options and poor prognosis.⁴¹

Key Takeaways:

- ✓ **BTKi are a standard option in patients with R/R MCL.**
- ✓ **Retrospective analyses of prospective studies suggest ibrutinib is most effective when used as second-line therapy in R/R MCL.**
- ✓ **There are no head-to-head comparisons between available covalent BTKi in R/R MCL, although in other B-cell malignancies, randomized comparisons between zanubrutinib and acalabrutinib demonstrate the second generation BTKi have lower rates of AEs than ibrutinib, with reduced toxicity, including cardiovascular toxicity.**

BCL-2 Inhibitors

The protein B cell leukemia/lymphoma-2 (BCL-2) is commonly overexpressed in B-cell NHL, including MCL, and causes dysregulation of apoptosis. Venetoclax is a highly selective BCL-2 inhibitor that was evaluated in a phase I study, which included a subgroup of 28 patients with R/R MCL and demonstrated an ORR of 75%, a CR rate of 21%, and a median PFS of 14 months. Most patients (56%) experienced grade 3-4 AEs, which were largely hematological. Five patients developed clinical tumor lysis syndrome (TLS).⁴² In a prospective phase II study, the combination of ibrutinib with venetoclax resulted in a CR rate of 42%, which was higher than historical CR rates with ibrutinib as monotherapy. TLS was observed in 2/24 patients and common AEs were low-grade non-hematological and grade 3-4 hematological events.⁴³ A recent phase I/II study investigated the use of ibrutinib, venetoclax, and obinutuzumab as a combination strategy in untreated or R/R MCL. The 2-year PFS in R/R patients was 69.5% and the 1-year PFS in untreated patients was 93.3%, showing high response rates.⁴⁴

Despite these data, the availability of venetoclax for MCL in Canada is limited and Health Canada has not yet approved this agent as monotherapy or in combinations, including BTKi, for use in MCL. Future prospective studies of BCL2 inhibitors are necessary to better understand the dosing, schedule, combinations, efficacy, and toxicity of these agents.

Chimeric Antigen Receptor T-Cell (CAR-T) Therapy

The anti-CD19 CAR-T product brexucabtagene autoleucel is approved by Health Canada for patients with R/R MCL after ≥ 2 lines of prior systemic therapies including a BTKi. This regulatory approval was based on the ZUMA-2 study, which showed an objective response rate of 91% in heavily pretreated patients, with a CR rate of 68% in the total population. At a median follow-up of 35.6 months, 37% of patients remained in remission. The median DOR was 28.2 months, with a median PFS of 25.8 months and median OS of 46.6 months. Common grade ≥ 3 AEs include cytopenia and infections. Grade ≥ 3 cytokine release syndrome (CRS) was observed in 15% of patients, and 31% experienced neurological events.^{45,46}

While CAR-T therapy is associated with significant cost and toxicity, it is also associated with a high rate of durable

remissions in patients who are refractory to other treatments including BTKi. A Canadian cost-effectiveness assessment found CAR-T therapy to be an effective use of healthcare resources relative to the best supportive care within its public health care system. Access to CAR-T, however, remains a challenge in many Canadian centers. Also, additional research is needed to confirm these results, especially with a longer length of follow-up.⁴⁷

Key Takeaways:

- ✓ **Anti-CD19 CAR-T therapy with brexucabtagene autoleucel is associated with high response rates with relatively long durability in patients with heavily pretreated R/R MCL, including prior BTKi therapy.**
- ✓ **Despite its high costs, CAR-T therapy may be a cost-effective option in Canada for eligible patients with R/R MCL.**

Chemotherapy

Chemotherapy strategies have limited efficacy in R/R MCL. For instance, a phase III study assessing temsirolimus vs investigator's choice as the control arm, mainly consisting of cytotoxic agents, revealed an ORR of 2% for the control arm.⁴⁸ A retrospective cohort study assessed the use of R-BAC (rituximab, bendamustine, cytarabine) in patients with MCL progressing on BTKi. The ORR was 83%, with a CR rate of 60% and 31% of patients were bridged to allogeneic stem cell transplant (allo-SCT), with only one patient relapsing after alloSCT, suggesting this strategy may be effective in selected patients with BTKi-relapsed MCL.⁴⁹ The concern with R-BAC is that it may not necessarily control R/R MCL in the long term. However, it may achieve rapid disease control in the short term and open a window for consolidative strategies, such as CAR-T or allo-SCT.

Proteasome inhibitors

Given the role of NF-KB in the growth and survival of MCL cells, the inhibition of this signaling pathway with proteasome inhibitors can result in cell cycle arrest and apoptosis. The proteasome inhibitor bortezomib has been associated with ORRs in patients with MCL ranging between 29 and 50%, with a very limited number of patients achieving a CR.⁵⁰⁻⁵³ A longer follow-up study revealed a median time to progression of 6.7 months, with a 61.1-month median OS.⁵⁴

Combining bortezomib with rituximab was not shown to improve ORR⁵⁵, while the combination of bortezomib and gemcitabine may improve ORR to 60%.⁵⁶ Finally, the combination of bendamustine, bortezomib, and rituximab has been investigated in a small study and was found to result in an ORR of 83%.⁵⁷ However, proteasome inhibitors were mainly in use before the availability of BTKi, and efficacy data for BTKi are better than for bortezomib. Therefore, for most patients with R/R MCL BTKi will be preferable over bortezomib.

Immunomodulatory imide drugs (IMiDs)

IMiDs are a class of drugs with immune-modulatory, anti-angiogenic, anti-inflammatory, and anti-proliferative properties. In patients who were ineligible for intensive chemotherapy or SCT, the IMiD lenalidomide resulted in an

8.7-month PFS, which was statistically significantly better than the 5.2-month PFS for those treated by the investigator's choice of treatment.⁵⁸ However, lenalidomide treatment is associated with significant grade 3-4 hematologic AEs, including neutropenia, with a risk of febrile neutropenia, thrombocytopenia, anemia, and lymphopenia, which may result in an increased risk of deadly infections.⁵⁸⁻⁶⁰ Similar to bortezomib, BTKi are also preferred prior to IMiDs. Lenalidomide can be considered after BTKi failure, although the expected efficacy remains low.

Allogeneic stem cell transplant (allo-SCT)

Finally, in patients with aggressive MCL, reduced-intensity conditioning (RIC)-allo SCT may provide long term disease control.⁶¹⁻⁶³ Patients with aggressive MCL with *TP53* alterations or 17p deletions, which are associated with aggressive disease and therapy resistance, may benefit from allo-SCT. A small retrospective study showed that allo-SCT could overcome the poor outcome associated with *TP53* alterations in patients who had received a median of 3 prior treatments, of whom 42% had received prior ibrutinib and 68% a prior auto-SCT.⁶⁴ About 25% of refractory patients achieve durable remissions after allo-SCT.⁶⁵ Patients with a sustained remission for >12 months after auto-SCT, may achieve long-term control after salvage allo-SCT.⁶⁶ For those patients relapsing post-allo-SCT, donor lymphocyte infusion may be an option.⁶¹

Key Takeaways:

- ✓ **A repeat course of rituximab-containing chemotherapy may be reasonable in patients who achieved a long treatment-free interval after front-line immunochemotherapy.**
- ✓ **Agents such as bortezomib or lenalidomide are associated with relatively low response rates and limited duration of benefit in R/R MCL but could be considered after failure or BTKi and/or CAR-T therapy.**
- ✓ **Allo-SCT can be considered in selected patients with R/R MCL after carefully weighing risks, benefits, and alternatives.**

Conclusion

Over the past decades, options for patients with MCL have expanded with the arrival of multiple new types of therapies, which have improved outcomes for many patients, although MCL remains incurable. Chemoimmunotherapy remains the standard of care for first-line therapy, including strategies such as auto-SCT in young and fit patients. Novel agents with activity in R/R MCL, such as BTKi, are quickly moving into the front-line setting and will likely influence the current decision-making algorithm. CAR-T cell therapy is highly active in patients with R/R MCL, including those who received prior BTKi therapy, although it has important cost, access, and toxicity considerations. Similarly, allo-SCT may be effective in a small subgroup of patients.

Despite these advances, treatment options remain limited for most patients with R/R MCL, especially in those with adverse biology disease, the very elderly/frail, and those who received

prior BTKi therapy. Bortezomib, BCL-2 inhibitors, IMiDs, and potentially a second course of chemoimmunotherapy may be effective, although response rates for these strategies are relatively low and unlikely to be sustained in the long term. Non-covalent BTKi such as pirtobrutinib⁶⁷, the ROR-1 antibody-drug conjugate zilovertamab⁶⁸, and variations of CAR-T therapies such as combined targeting of CD19 and CD20⁶⁹, are more likely to emerge as the next generation of active therapies in R/R MCL that will again influence treatment sequencing and combinations and hopefully improve outcomes and quality of life.

Key Conclusions:

- ✓ **Despite novel treatments and combinations, MCL remains incurable.**
- ✓ **Front-line treatment choices are largely based on patients' age, fitness and disease biology (Figure 1).**
- ✓ **Preferred treatment options for R/R MCL include BTKi and CAR-T cell therapy.**
- ✓ **Other treatment options for R/R MCL include chemoimmunotherapy, bortezomib, IMiD, BCL-2 inhibitors, and allogeneic SCT.**
- ✓ **Additional therapies for R/R MCL with different mechanisms of action are currently being evaluated in prospective studies.**

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