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Front-Line Management of Mantle Cell Lymphoma in Canada: A Practical, Risk-Adapted Approach

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Introduction

Mantle cell lymphoma (MCL) is a mature B-cell non-Hodgkin lymphoma (NHL) that accounts for approximately 5–7% of all lymphomas.[1] Its clinical presentation is heterogeneous, ranging from an indolent leukemic non-nodal subtype that may be managed with observation to highly aggressive disease characterized by *TP53* alterations, blastoid or pleomorphic morphology, and high Ki-67 expression. Although relatively uncommon, an estimated 500–600 new cases are diagnosed annually in Canada,[2] underscoring the importance of optimizing evidence-based management strategies. In this review, we discuss front-line treatment approaches for MCL within the Canadian practice landscape.

Indolent MCL

Approximately 10–15% of patients with MCL have indolent disease biology based on clinical and/or pathological features. An illustrative example is the leukemic non-nodal subtype, which is often SOX11-negative and presents with predominant bone marrow, peripheral blood, and splenic involvement. Nodal MCL can also exhibit an indolent behaviour, particularly when associated with low tumour burden, low Ki-67, and classic histology. Several studies have shown that these patients can be safely observed without compromising long-term outcomes.[3-5]

Limited-Stage MCL

True limited-stage MCL (non-bulky stage I–II) is uncommon, accounting for only about 5% of cases. Comprehensive staging with positron emission tomography/computed tomography (PET/CT), bone marrow biopsy, and gastrointestinal endoscopies is required to confirm limited-stage MCL, as bone marrow involvement is common and gastrointestinal involvement occurs in nearly 90% of patients.[6-8] Once limited-stage disease is confirmed, localized radiotherapy (4–24 Gy) may be considered, as retrospective series have reported high response rates and durable remissions.[9–11] Initial observation is also a reasonable approach for patients with asymptomatic disease, as clinical outcomes appear broadly similar to those of patients treated upfront.[3,12]

Advanced Stage MCL

Younger and Fit Patients

For the last two decades, the treatment of younger and fit patients has relied on intensive chemoimmunotherapy induction, followed by autologous stem cell transplant (ASCT) consolidation and maintenance rituximab (M-R). Although there is no strict age cut-off, this approach is generally reserved for patients younger than 65–70 years without significant medical comorbidities. Various induction regimens have been studied, including R-maxi-CHOP alternating with R + high-dose cytarabine,[13] 3 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by 3 cycles of R-DHAP (rituximab, dexamethasone, cisplatin, and cytarabine),[14] 6 cycles of alternating R-CHOP/R-DHAP,[15] and R-DHAP x4.[16] These induction regimens yield overall response rates (ORRs) above 90% with complete response (CR) rates above 50%, with no regimen appearing clearly superior. Importantly, R-CHOP/R-DHAP was associated with an overall survival (OS) advantage compared to R-CHOP in the long-term follow-up of the MCL Younger Trial.[17]

Bendamustine and rituximab (BR) with ASCT and M-R is also a feasible front-line strategy

for younger, transplant-eligible patients.[18,19] A retrospective study conducted at BC Cancer compared 97 patients treated with BR to 232 patients treated with R-CHOP/R-DHAP in the MCL Younger trial.[20] The ORR was 90% (54% CR) with BR and 94% (54% CR) with R-CHOP/R-DHAP, with similar proportions of patients proceeding to ASCT (77% and 78%, respectively). There were no significant differences in progression-free survival (PFS) on unadjusted (hazard ratio [HR]: 0.87, 95% confidence interval [CI]: 0.53–1.41, p=0.56) or adjusted analyses (HR: 0.79, 95% CI: 0.45–1.37, p=0.40), suggesting that BR followed by ASCT and M-R may achieve outcomes comparable to R-CHOP/R-DHAP with ASCT, with the caveat that M-R was rarely incorporated in the latter regimen.

The benefit of ASCT consolidation after intensive induction in MCL is supported primarily by phase II studies, which reported 4–5-year PFS and OS rates of 56–73% and 64–81%, respectively.[14,21] However, the relative contribution of intensive induction versus ASCT to these outcomes remains unclear. The only randomized trial evaluating ASCT (post-CHOP-like induction) demonstrated a significant improvement in PFS (39 vs. 17 months), although no OS benefit was observed.[22] Similarly, in the MCL Younger trial, ASCT was associated with higher rates of minimal residual disease (MRD)-negativity,[15] a known predictor of survival.[23] Beyond transplantation itself, post-ASCT maintenance strategies may further improve disease control. In the LYMA trial, maintenance rituximab administered every 2 months for 3 years significantly improved survival, with 4-year PFS/OS of 83%/89% versus 64%/80% with observation.[16]

The role of consolidative ASCT has recently been challenged in two practice-changing clinical trials. The TRIANGLE study assessed whether ASCT could be omitted when introducing ibrutinib, a covalent Bruton's tyrosine kinase inhibitor (cBTKi), in the induction and maintenance phases of therapy. Patients were randomized to either R-CHOP/R-DHAP followed by ASCT (arm A), ibrutinib-R-CHOP/R-DHAP followed by ASCT and ibrutinib maintenance (arm A+I), or ibrutinib-R-CHOP/R-DHAP followed by ibrutinib maintenance alone (arm I). In the primary analysis, this study showed that arm A was not superior to arm I (3-year failure-free survival (FFS) of 72% vs. 86%; p=0.9979).[24] In the 4-year follow-up analysis, TRIANGLE confirmed the superiority of arm I over arm A for both FFS and OS, and showed that adding ASCT to the ibrutinib-containing regimen (arm A+I) did not prolong FFS. Moreover, ASCT plus ibrutinib (arm A+I) was associated with significantly higher rates of grade 3–5 hematologic toxicities and infections during maintenance and follow-up compared with ibrutinib alone (arm I).[25]

In the ECOG-ACRIN EA4151 trial, patients with MCL in complete remission after any induction regimen underwent PET/CT, bone marrow biopsy, and peripheral blood MRD-testing by clonoSEQ. Patients in CR with undetectable MRD (10^{-6}) were randomized to ASCT and 3 years of M-R (arm A) or 3 years of M-R alone (arm B). Patients with MRD-positive CR (arm C) or MRD-indeterminate CR (arm D) both received an ASCT and 3 years of M-R. When comparing arms A and B, the estimated OS HR was 1.11 (95% CI: 0.71-1.74; p=0.66) and the estimated PFS HR was 1.05 (95% CI: 0.71–1.56; p=0.79), confirming the lack of benefit of ASCT in patients in CR with undetectable MRD.[26]

Canadian perspective: For younger and fit patients, a TRIANGLE-based strategy incorporating R-CHOP plus ibrutinib alternating with R-DHAP, followed by two years of ibrutinib and three years of M-R without ASCT, would be preferred when there is access to a BTKi. In settings where BTKi are unavailable, cytarabine-containing induction or BR remain reasonable alternatives, with the decision to pursue consolidative ASCT guided by MRD status if possible. Rituximab maintenance should be offered to all patients.

Older or Unfit Patients

In patients who are not suitable for ASCT, rituximab-based chemoimmunotherapy followed by M-R has remained the standard of care until very recently. Several rituximab-containing regimens have been evaluated, including R-CHOP, BR, R-BAC (rituximab, bendamustine, and cytarabine), and VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone). In the European MCL Elderly study, R-CHOP was associated with an improved median OS compared with FCR (fludarabine, cyclophosphamide, and rituximab; 6.4 vs. 3.9 years). Among responders, maintenance rituximab further prolonged OS compared with interferon maintenance (9.8 vs. 7.1 years).[27,28]

R-CHOP was later compared to BR in two randomized studies in indolent NHL. The BRIGHT

trial (including patients with MCL) showed a PFS benefit favouring BR (5-year PFS HR: 0.61, 95% CI 0.45–0.85; p=0.0025),[29] confirmed in the phase III StiL trial (median PFS 69.5 vs. 31.2 months; HR: 0.58, 95% CI: 0.44–0.74; p<0.0001).[30] Given that both studies were conducted without M-R, the phase II StiL MAINTAIN trial randomized patients to M-R versus observation after BR, showing no PFS benefit.[31] However, real-world studies later demonstrated improved outcomes with M-R, as highlighted in a retrospective analysis of 4,216 patients with MCL, showing longer time to next treatment (HR: 1.96, 95% CI: 1.61–2.38; p<0.001) and improved OS (HR: 1.51, 95% CI: 1.19–1.92; p<0.001).[32] These findings were later supported by another large retrospective study of 911 patients across 27 US and Canadian academic centres, with M-R associated with longer median event-free survival (EFS: 49.9 months vs. 29.7 months; p<0.001) and OS (109.5 vs. 74.2 months; p<0.001).[33]

Two recent phase III trials have evaluated the incorporation of a covalent BTKi into BR and maintenance rituximab in the first-line treatment of ASCT-ineligible patients. The SHINE trial evaluated ibrutinib in combination with BR,[34] whereas the ECHO trial evaluated acalabrutinib in combination with BR.[35] Both studies showed that the addition of a cBTKi to BR and rituximab maintenance improves PFS but not OS. In the SHINE trial, there was a trend toward inferior OS in the ibrutinib arm, largely driven by an increased number of toxicity-related mortality. This was not observed in the ECHO trial, where a trend toward improved OS was seen in the experimental arm despite a 69% crossover rate. Interestingly, all patients appeared to benefit from the addition of a cBTKi regardless of their risk profile (blastoid/pleomorphic, TP53-mutant, Ki-67 >30%, high-risk MCL International Prognostic Index [MIPI]).

A key question is whether BR plus acalabrutinib upfront is superior to a sequential strategy of BR followed by acalabrutinib at relapse, particularly given that 69% of patients in the ECHO control arm received acalabrutinib at progression. However, real-world data suggest that not all patients survive to receive second-line therapy. In an Australian observational study, approximately 7% of patients with MCL died before second-line treatment,[36] while in a population-based study from Ontario, 39.3% of patients died following front-line therapy,[37] supporting the rationale for incorporating a cBTKi into initial treatment. Conversely, a multicentre study led by Mayo Clinic evaluated event-free survival 2 (EFS2) in 203 patients with MCL treated with front-line BR followed by a second-line cBTKi.[38] Using this sequential approach, the median EFS2 was 64.8 months (95% CI: 56.7–82.8), which is comparable to the median PFS of 66.4 months observed in the BR–acalabrutinib arm of ECHO. Therefore, given the higher risk of infectious and cardiovascular toxicities associated with adding a cBTKi, its use should be carefully weighed in older or frail patients but strongly considered in patients with higher-risk disease.

Finally, the phase III ENRICH trial compared a chemotherapy-free regimen (ibrutinib-rituximab) to standard chemoimmunotherapy (investigator's choice of BR or R-CHOP) in patients aged >60 years with untreated MCL.[39] After a median follow-up of 47.9 months, ibrutinib-rituximab was associated with superior PFS relative to immunochemotherapy (adjusted HR: 0.69, 95% CI: 0.52–0.90; p=0.0034). This benefit was only observed in comparison to the R-CHOP subgroup (HR: 0.37, 95% CI: 0.22–0.62) and not the BR subgroup (HR: 0.91, 95% CI: 0.66–1.25). Given the lower incidence of grade 3–4 neutropenia and the faster improvement in quality of life, the authors suggested that IR should be considered a new standard-of-care option for older adults with untreated MCL. Of note, this regimen should not be used for patients with blastoid disease, in whom a trend in favour of immunochemotherapy was observed (median PFS: 6.9 months vs. 21.1 months).

Canadian perspective: For older or unfit patients, BR plus acalabrutinib induction followed by two years of rituximab maintenance and continuous acalabrutinib until progression or unacceptable toxicity would be our preferred approach, particularly for those with higher-risk features (TP53 mutation, blastoid or pleomorphic morphology, Ki-67 >30%, or high-risk MIPI). In patients with low biological risk or significant concerns for cardiovascular or infectious toxicities, BR followed by rituximab maintenance or a chemotherapy-free approach with cBTKi–rituximab (2nd generation cBTKi preferred), followed by rituximab maintenance and continued cBTKi until progression or unacceptable toxicity, remain reasonable alternatives.

Frail Patients

Frail patients are more likely to experience treatment-related toxicity and poor outcomes.

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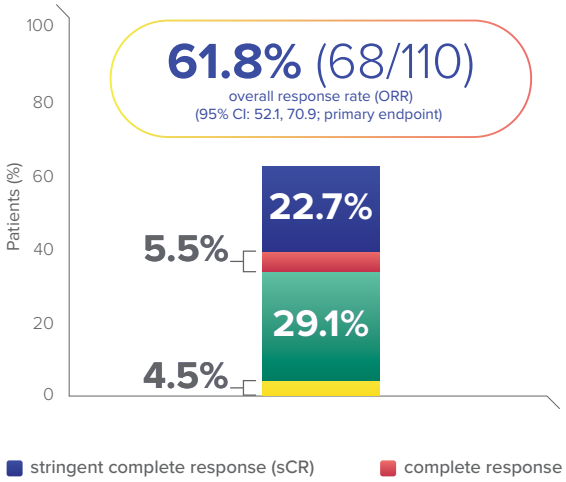

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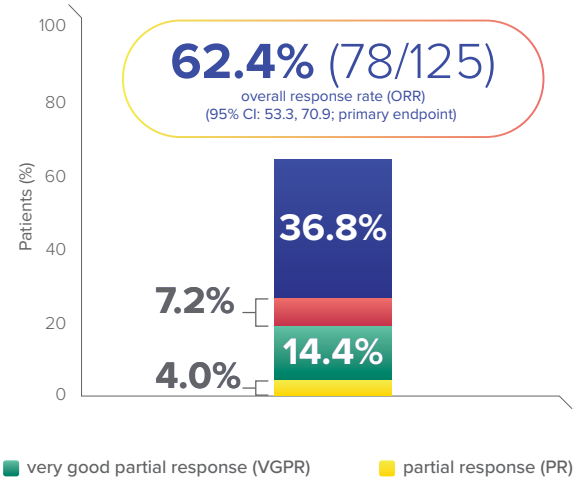

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55.1% of the 78 responders in the MajesTEC-1 trial switched from weekly to biweekly dosing during the study[1]

For those who remain eligible for chemotherapy, options include R-chlorambucil, R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), and attenuated R-CHOP or BR. A retrospective study conducted in the UK and Ireland reported outcomes of these regimens in 95 patients who were unfit for full-dose BR or R-CHOP.[40] The median PFS was 15 months, and patients treated with attenuated R-CHOP/BR had a superior PFS than those treated with R-chlorambucil/R-CVP (HR: 0.49; p=0.02) at the expense of more toxicity-related hospitalizations.

Chemotherapy-free approaches, such as ibrutinib-rituximab (ENRICH trial), acalabrutinib-rituximab (ALTAMIRA trial), and cBTKi monotherapy, are reasonable options for this patient population. In the multicenter phase II ALTAMIRA trial, investigators evaluated the safety and efficacy of acalabrutinib plus rituximab in elderly patients, achieving an ORR of 95% (61% CR), with a 1-year PFS and OS of 86.5% and 92.9%, respectively. These outcomes were significantly improved compared with matched real-world controls treated with standard therapies, supporting this combination as a front-line option.[41]

TP53-Mutated MCL

TP53-mutated disease is often associated with rapid progression, suboptimal response to standard chemoimmunotherapy, and poor survival outcomes.[42] Clinical trials or triple-therapy regimens incorporating an anti-CD20 monoclonal antibody, a cBTKi, and a BCL2 inhibitor should therefore be considered when available. The phase II BOVen trial evaluated zanubrutinib, obinutuzumab, and venetoclax in patients with untreated MCL harbouring *TP53* mutations, using an MRD-driven approach.[43] Despite its small sample size (n=25), outcomes were highly favourable, with an ORR of 96%, CR rate of 88%, and high MRD-negativity rates (95% at 10^{-5} sensitivity; 84% at 10^{-6}). With a median follow-up of 28.2 months, the 2-year PFS and OS were 72% and 76%, respectively.

References: 1. TECVAYLI® (teclistamab injection) Product Monograph. Janssen Inc. June 26, 2025. **2.** Data on file, Johnson & Johnson. October 13, 2023. **3.** Data on file, Johnson & Johnson. October 31, 2025.

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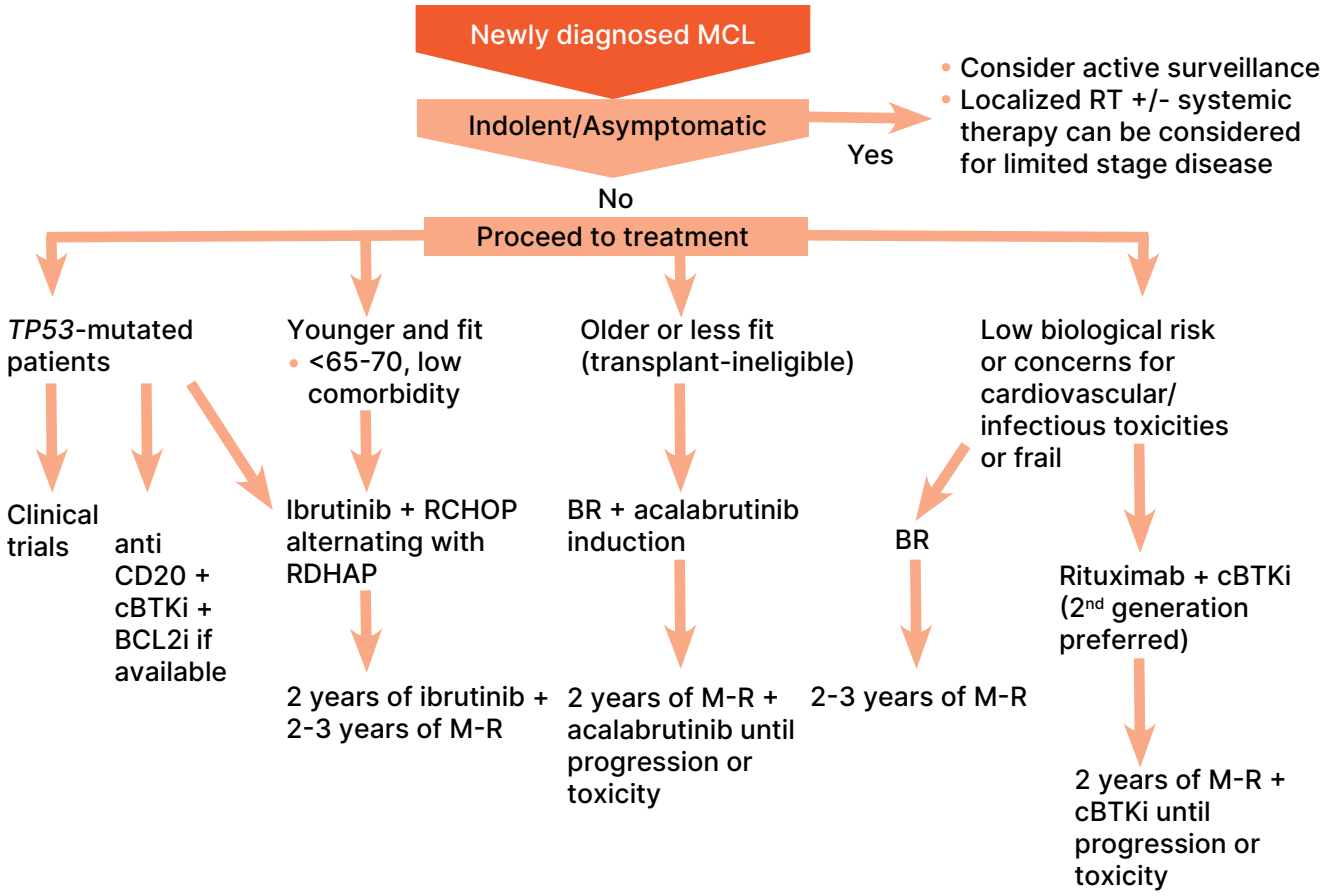

Figure 1. Proposed treatment algorithm for MCL in Canada in 2026; *courtesy of Justin Desroches, MD, FRCPC and Diego Villa, MD, MPH, FRCPC.*

Consistent with these findings, similar efficacy has been observed with an alternative triplet combination. In the phase II TRAVERSE trial evaluating acalabrutinib, venetoclax, and rituximab (AVR) in treatment-naïve MCL, the subgroup of patients with *TP53* mutations demonstrated high response rates, including an ORR of 88.2%, a CR rate of 64.7%, and MRD-negativity in 94.1% during induction.[44] Finally, in the treatment-naïve subgroup of the SYMPATICO trial, patients with *TP53* mutations also demonstrated meaningful responses to the ibrutinib–venetoclax doublet, with an ORR of 90%, a CR rate of 55%, a median PFS of 22.0 months, and a 3-year OS of 68%.[45]

Canadian perspective: Clinical trials or triple-therapy regimens should be offered to TP53-mutated patients. If these are not available, a TRIANGLE approach (younger/fit patients) or ECHO approach (older/unfit patients) would be recommended.

Future Directions and Conclusion

The front-line management of MCL is undergoing a rapid transition from chemotherapy-intensive approaches toward targeted treatment strategies. Among these, cBTKi are most likely to remain a central component of therapy. Data from TRIANGLE, ECHO, and ENRICH support the incorporation of these agents into front-line regimens across multiple patient populations, including transplant-eligible and transplant-ineligible patients. However, their optimal use may evolve away from prolonged maintenance therapy toward time-limited combinations aimed at achieving deep and durable remissions.

BCL2 inhibitors are also emerging as key partners in combinations with cBTKi. Early-phase studies evaluating combinations of anti-CD20 monoclonal antibodies, cBTKi, and venetoclax have demonstrated high rates of CR and MRD-negativity, particularly in

high-risk populations such as those with *TP53* mutations. These regimens raise the possibility of fixed-duration, MRD-guided treatment strategies, which may reduce long-term toxicity while preserving efficacy. Ongoing studies will determine whether such approaches can be generalized beyond high-risk subsets and ultimately challenge current continuous cBTKi maintenance therapy models.

Additionally, the role of chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies in the front-line setting is under investigation. Earlier integration of T-cell-directed therapies, as explored in the CARMAN,[46] WINDOW-3,[47] and GLOVe trials,[48] may enhance efficacy by capitalizing on improved T-cell fitness and lower disease burden. While their efficacy in relapsed/refractory MCL is well established, their use in front-line therapy is currently limited by logistical complexity, cost, and the emergence of highly effective targeted combinations. Nevertheless, front-line T-cell-directed therapies may have a future role in selected high-risk populations or as an early consolidation strategy in patients with detectable MRD following induction therapy.

Taken together, the front-line management of MCL continues to evolve with the integration of cBTKi, MRD-guided strategies, and emerging novel agents. In Canada particularly, treatment decisions must balance clinical efficacy, toxicity, and access to publicly funded therapies.

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BCL2 =B-cell lymphoma 2.

* Comparative clinical significance is unknown.

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