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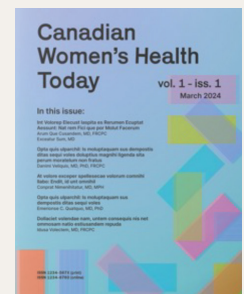
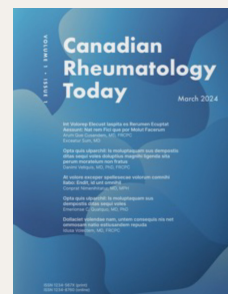
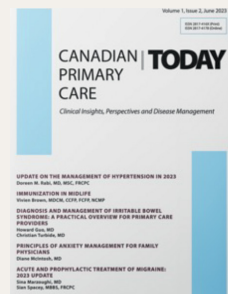
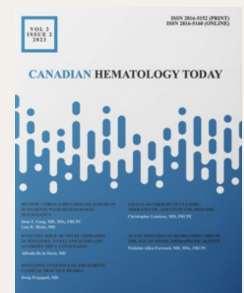
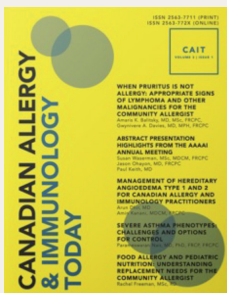
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Front-line Management of Follicular Lymphoma

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Introduction

Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma (NHL) in Western countries. Most patients have an indolent disease course with 10-year survival estimates of 80% among all patients in the rituximab era.¹ However, risk stratification schema can identify subgroups of patients at higher risk of early death and/or progression following front-line therapy. In addition, histologic transformation to an aggressive NHL occurs in approximately 2% of patients per year.¹ Many patients can initially be observed, but ultimately, most will be treated with multiple lines of therapy during their lifetimes. Current Health Canada-approved systemic treatment options include chemoimmunotherapy and lenalidomide plus rituximab. Phosphoinositide 3-kinase (PI3K) inhibitors were initially approved but were later withdrawn because of toxicity considerations. Newer therapies likely to impact care in Canada include bispecific T cell engagers (BiTEs) and chimeric antigen receptor (CAR)-T cell therapy.

Biology as it Pertains to Targeted Therapies

Several new targeted therapies have been developed for B cell NHL (**Table 1**). These targeted therapies have been developed based on an understanding of the role of several intracellular pathways in the pathogenesis of B cell lymphomas. Agents that target the NF- κ B pathway, such as PI3K inhibitors or Bruton's tyrosine kinase inhibitors (BTKi), anti-apoptotic pathways, such as B cell lymphoma 2 (BCL2), or the enhancer of zeste homolog 2 (EZH2) methylation factor have been explored. In addition, non-specific reagents that enhance innate immune activation, such as immunomodulating drugs (IMiDs)—which may also have direct cytotoxic effects—and monoclonal

antibodies targeting B cell-specific antigens have also been studied. We are beginning to see treatment combinations of several of these agents being explored.

Grading, Staging, Prognostic Indices, and Outcome

In the recently updated World Health Organization (WHO) classification of lymphomas, grading of FL is no longer considered mandatory because clinical outcomes among grades 1, 2, and 3A are not substantially different in the modern era.² Instead, these three are now referred to as “classic FL,” whereas grade 3B is referred to as Follicular Large B Cell Lymphoma and is generally treated as diffuse large B cell lymphoma (DLBCL).

Given the prolonged survival of patients with FL, it is pertinent to identify patients at higher risk of progression following first-line therapy, histologic transformation, and early death. The Follicular Lymphoma International Prognostic Index (FLIPI) was developed in the pre-rituximab era to predict overall survival (OS), and incorporates age, stage, hemoglobin level, lactate dehydrogenase level, and the involvement of more than four nodal sites. It stratifies patients into low, intermediate, and high risk, characterized by an estimated 10-year OS of 71%, 51%, and 36%, respectively.³ The FLIPI has been validated in a modern cohort of patients treated with chemoimmunotherapy (e.g. bendamustine and rituximab), even though current outcomes have numerically improved compared to this original model.⁴ The newer FLIPI2 model was developed to predict progression-free survival (PFS) among a cohort of patients treated with rituximab and incorporates age, hemoglobin level, bone marrow involvement, longest diameter of the largest involved lymph node, and β 2-microglobulin. By the FLIPI2, low, intermediate, and high-risk patients had a 5-year PFS of 79%, 51%, and 20%, respectively; and a 5-year OS of

Location	Target	Reagent	Health Canada approved	Funding
Cell surface	CD20	Rituximab	yes	Broad funding for induction and maintenance for IV and SC
		Obinutuzimab	yes	Chemotherapy obinutuzimab and obinutuzimab maintenance, Stage II bulky, Stage III and IV FL
		Radiolabelled mAbs	yes	Not funded for FL
	CD20xCD3	Mosunetuzumab, Glofitmab, Epcoritamab	Not approved for FL Glofitmab and Epcoritamab HC approved for R/R DLBCL	Not funded
	CD19	CAR-T	Axicel approved for R/R FL	Funding recommended in Ontario
Intracellular	MYD88	BTK inhibitors	Not approved for NHL	Not funded for FL
	PI3K	Idelalisib	Not approved for NHL	Not funded for FL
	EZH2	Tazemetostat	Not approved for FL	Not funded for FL
	Cereblon	Lenalidomide	Not approved for FL	Not funded for FL
	BCL2	Venetoclax	Not approved for FL	Not funded for FL
Microenvironment	Adaptive immune system	Lenalidomide	Not approved for FL	Not funded for FL
	T cells	Bispecific antibodies CAR-T cells	Axi-cel approved for R/R FL	Funding recommended in Ontario

Table 1. Biologic targets and associated treatments for FL; *courtesy of Samantha Hershenfeld, MD, FRCPC, Jennifer Teichman, MD, FRCPC, and Neil L. Berinstein, MD, FRCPC.*

Abbreviations: BTK: Bruton's tyrosine kinase; CAR: chimeric antigen receptor; DLBCL: diffuse large B cell lymphoma; FL: follicular lymphoma; HC: Health Canada; IV: intravenous; mAbs: monoclonal antibodies; R/R: relapsed/refractory; SC: subcutaneous

98%, 88%, and 77%, respectively. Interestingly, β 2-microglobulin, which is absent from the FLIPI model, was considered the covariate with the greatest prognostic weight in the FLIPI2 model.⁵

Recurrent genetic mutations cooperate with BCL2 translocations to drive lymphomagenesis in FL. The M7-FLIPI was therefore developed to integrate clinical and molecular risk factors to further improve prognostication among high-risk patients.⁶ It was developed from a cohort of patients with advanced-stage disease who were treated with R-CHOP/R-CVP (cyclophosphamide, doxorubicin, prednisone, rituximab, and vincristine/ rituximab, cyclophosphamide, vincristine, and prednisone). The M7-FLIPI includes the FLIPI score, Eastern cooperative oncology group (ECOG) performance status, and seven recurrently mutated genes (*EZH2*, *ARID1A*, *MEF2B*, *EP300*, *FOXO1*, *CREBBP*, and *CARD11*). The model identified a high-risk and a low-risk group, with a five-year failure-free survival of 38% versus 77%, respectively. The M7-FLIPI reclassified about half of patients with a high-risk FLIPI score into the low-risk M7-FLIPI category due to the presence of favourable risk mutations, particularly in *EZH2*. However, in a separate analysis of the GALLIUM trial, the M7-FLIPI was not prognostic in patients treated with bendamustine-based therapy, likely due to a reversal of the prognostic impact of *EZH2* mutations in that setting.⁷ In light of this and limitations in access to DNA sequencing, the M7-FLIPI is not currently used in routine clinical practice in Canada.

None of these models have been validated as tools to select or adapt treatment in FL. Furthermore, they are not used dynamically throughout a patient's disease course. Disease progression within 24 months following front-line chemoimmunotherapy (POD24) is a poor prognostic factor that predicts inferior OS.⁸ Currently, the FLIPI and FLIPI-2 are commonly used to prognosticate in real-world clinical settings, but newer dynamic and treatment-adaptable models are needed.

Treatment Approach-Overall

a. Localized Disease:

The rare patient presenting with localized follicular lymphoma may be treated with curative intent involved-field radiation therapy (IFRT). However, long-term follow-up of these patients

has demonstrated late relapses (≥ 10 years) in up to 50% of patients. Recurrences typically occur outside of radiation fields, in patients with larger initial tumours, and are more likely to occur in those with stage 2 versus stage 1 disease.⁹ Positron emission tomography (PET) staging prior to treatment upstages some patients and better identifies those with localized disease. High response rates and durable remissions can be achieved with low dose IFRT (4 Gy in two fractions); however, randomised data suggests that 24 Gy in 12 fractions may be more effective for preventing relapse.^{10,11} Alternatives include observation for asymptomatic patients, particularly for older patients, or initiation of chemotherapy for patients with bulky or non-contiguous and symptomatic early-stage disease.

b. Low Volume Advanced:

These patients may be monitored without treatment. Three randomised controlled trials have shown no survival advantage for early versus delayed initiation of therapy in asymptomatic patients.¹²⁻¹⁴ Watchful waiting was compared to rituximab monotherapy with or without maintenance rituximab.¹⁵ Time to initiation of new therapy (chemotherapy or radiation) was delayed in the two arms that received rituximab and quality of life was improved in the rituximab maintenance arm. In a Canadian context, rituximab induction in asymptomatic patients is more cost-effective than watchful waiting or rituximab induction plus maintenance¹⁶; however, whether delaying time to next treatment is clinically meaningful is questionable. The Resort trial showed that retreatment with rituximab in patients with low volume, advanced-stage disease previously treated with rituximab is as effective as maintenance rituximab in delaying the time to chemotherapy, but required considerably less rituximab use.¹⁷

c. High Volume Advanced:

Treatment for high-volume advanced disease is often delayed until one of the groupe d'étude des lymphomes folliculaires (GELF) criteria is met.¹³ The standard of care chemotherapy in most geographical locations for patients with symptomatic advanced disease is bendamustine and rituximab (BR). In the StiL and BRIGHT trials, BR outperformed R-CHOP with a more favourable toxicity profile.^{18,19} Lymphopenia and susceptibility to infections are increased with BR. The PRIMA trial demonstrated a PFS benefit

Stage	Recommended treatment	Alternative treatments	Comments
Stage 1 or 2 contiguous and low volume	IFRT	Observation rituximab	24 Gy in 12 fractions has higher cure rate ¹⁰ , but 4 Gy in 2 fractions is effective palliation. ¹¹
Stage 2 non-contiguous or high volume (>3 cm)	Observation	IFRT palliation, Rituximab monotherapy	Maintenance rituximab can be added.
Stage 3, 4-asymptomatic	Observation ¹⁴	Rituximab monotherapy ¹⁵	Maintenance can be added but retreatment at relapse is acceptable. ¹⁷
Stage 3, 4-symptomatic (GELF criteria)	BR ¹⁸	R-CHOP, R-CVP O-chemo and O maintenance are more active but more toxic. ²³	Lenalidomide + rituximab is a non-funded, equally effective option. ²⁷
	Maintenance Rituximab ²⁰	Maintenance Obinutuzumab	In patients with higher risk of infections or CR to front-line, or in pandemic maintenance call be shortened or eliminated Obinutuzumab is a non-funded option that cannot be given subcutaneously.

Table 2. Acceptable front-line therapies in Canada; courtesy of Samantha Hershenfeld, MD, FRCPC, Jennifer Teichman, MD, FRCPC, and Neil L. Bernstein, MD, FRCPC.

Abbreviations: BR: bendamustine + rituximab; CR: complete response; IFRT: involved-field radiation therapy; GELF: groupe d'étude des lymphomes folliculaires; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP: rituximab, cyclophosphamide, doxorubicin, prednisone

of maintenance rituximab after CVP or CHOP, with 51% of patients who received maintenance alive without progression at 10 years.^{20,21} It is not known whether rituximab maintenance improves PFS after BR treatment. Rituximab monotherapy followed by four maintenance infusions every two months can produce durable remissions in a subset of chemo-naïve patients with non-rapidly progressing disease.²²

Obinutuzumab, the glycol-engineered anti-CD20 monoclonal antibody, was compared to rituximab in combination with either bendamustine, CVP, or CHOP as front-line therapy in the Phase III GALLIUM trial.²³ Obinutuzumab demonstrated modestly improved PFS (3 year-PFS

of 80% versus 73.3%, $p=0.66$), higher rates of minimal residual disease (MRD), and PET negativity, as well as decreased POD 24, as compared to rituximab. The OS was not different between the arms in this trial. Obinutuzumab was associated with more frequent grade ≥ 3 adverse events (76% versus 67.8%), serious adverse events (46.1% versus 39.9%), and infusion reactions (59% versus 48.9%, $p=.001$). Given these modest incremental benefits and higher toxicity profile, obinutuzumab was not recommended for funding to use in the front-line management of FL in Canada.

There are comparable pharmacokinetic and clinical efficacy results with intravenous versus

subcutaneous rituximab²⁴ but a subcutaneous formulation of obinutuzumab is not available.

Rituximab has also been used as monotherapy in patients with advanced stage symptomatic FL. In the SAKK trial, 64 chemotherapy-naïve patients were randomly assigned to four doses of rituximab monotherapy with or without four additional doses given at two-month intervals.²² The event-free survival was longer in the prolonged rituximab arm with 45% of patients showing no disease progression at 8 years, suggesting that this therapy could be offered to advanced stage FL in cases where a rapid response to therapy was not required.

Radioimmunotherapy has been studied as front-line therapy for FL both as monotherapy or as adjuvant therapy after initial chemotherapy for advanced symptomatic disease. Bexxar (¹³¹I-tositumomab) did not show improved PFS when compared to rituximab after R-CHOP chemotherapy. Zevalin (⁹⁰Y-ibritumomab tiuxetan) resulted in a 36-month improvement in PFS compared to placebo after combination chemotherapy, but most patients did not receive initial R-chemotherapy. Given the limitations with the above results, radioimmunotherapy has not been widely used.²⁵

Although a long PFS has been observed after front-line high-dose therapy and autologous stem cell transplant with 50% of patients being disease-free at 10 years, no plateau in the survival curve has been documented.²⁶ In addition, a relatively high incidence of second malignancies, including myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and solid tumours, has dampened the enthusiasm for this approach.

d. Chemotherapy-Free Options-Targeted Therapies:

The RELEVANCE trial compared rituximab and lenalidomide (R2) to R-chemotherapy (investigator's choice of either CHOP (72%), bendamustine (23%) or CVP (5%).²⁷ PFS at 6 years was 60% for R2 and 59% for R-chemotherapy, and OS at 6 years was identical at 59% in both groups. There were more cytopenias, fatigue, nausea, vomiting, and peripheral neuropathy in the R-chemotherapy group, while the R2 group had more diarrhea, rash, and cutaneous reactions. These results suggest R2 is a chemotherapy-free option with similar results to chemotherapy and may be well-suited for patients who are more frail or older. The combination of lenalidomide and rituximab has also been compared to

rituximab monotherapy in the SAKK35/10 trial for symptomatic advanced-stage patients.²⁸ The most recent update from the American Society of Hematology (ASH) 2023 Annual Meeting showed a median PFS of 9.3 years in the lenalidomide rituximab group compared to 2.3 years with rituximab monotherapy.²⁹ Although not studied in a randomised trial, treatment with lenalidomide and obinutuzumab in the Phase Ib/II GALEN trial demonstrated impressive results with a 92% ORR and a CR at 30 months of 63% compared to 48% in the RELEVANCE trial.³⁰

Although BTKi have had limited activity as monotherapy in recurrent disease, they have been studied in combination with anti-CD20 monoclonal antibodies in the front-line setting. In the Phase II PCYC-1125-CA trial, concurrent ibrutinib and rituximab was compared to a two-month lead-in of ibrutinib followed by ibrutinib and rituximab.³¹ In the concurrent arm, the objective response rate (ORR) was 85% (40% complete response [CR]); however, the PFS at 30 months was 67%, which is inferior to the PFS seen in the RELEVANCE trial with R2. BTKi adverse events included bleeding in 40% of patients, although grade 3–4 bleeding occurred in only 2.5%, and cardiac events in 14% of patients.

Trials with different durations of treatment with rituximab and ibrutinib and with obinutuzumab combined with venetoclax are underway.

e. Novel Targeted Therapies in the Front-Line:

There has been an attempt to intensify treatment with targeted therapies in high-risk patients in the front line. Tazemetostat has shown activity in relapsed and refractory FL-particularly in patients with *EZH2*-mutated disease.³² A recent abstract presented at the ASH 2023 Annual Meeting examined R-CHOP and tazemetostat (an *EZH2* inhibitor), followed by maintenance with tazemetostat and rituximab in the front-line for higher-risk FL. Seventy-nine percent of patients achieved a complete metabolic response after induction therapy, and 18-month PFS and OS rates were 89.3% and 98.3%, respectively.³³

Early Phase I and II trials are currently examining novel immunotherapies such as BiTEs in the first line. Subcutaneous mosunetuzumab was given as monotherapy for 8 cycles in patients with stage II-IV FL and indications for treatment based on GELF criteria. Of the 26 patients thus far evaluable for response, the best ORR was 96% and CR was 81%.³⁴ A similar ongoing study

is examining mosunetuzumab in combination with lenalidomide for 12 cycles in first-line FL. In 27 patients evaluable thus far, the ORR was 88.9% and CR rate 81.5%.³⁵ About half of patients developed cytokine release syndrome in both trials, but all cases were low-grade. Despite the promising results, current follow-up is short, and BiTEs are not currently approved in the front-line setting by Health Canada. A summary of ongoing and completed clinical trials for novel agents in the front-line setting, as well as promising treatments in the relapsed/refractory setting, are summarized in **Table 3**.

f. Maintenance Therapy:

Because advanced-stage FL is incurable, strategies to delay relapse have been pursued, predominantly with anti-CD20 monoclonal antibodies. Several trials showed that rituximab maintenance improved outcomes in patients with symptomatic high-volume FL after various R-chemotherapy combinations. Longer-term follow-up of the PRIMA trial showed a median PFS of 10.5 years versus 4.1 years in favour of maintenance rituximab. OS was not improved. A meta-analysis of 2,315 patients from 11 randomised trials showed an OS benefit to maintenance therapy.³⁶ The OS benefit was greatest in patients receiving maintenance rituximab after second-line therapy. However, there are toxicities associated with rituximab maintenance, including B cell depletion, hypogammaglobulinemia, and rarely neutropenia and immune-related pneumonitis. The B cell depletion reduces immune reactivity to active vaccination, and only 10% of patients were found to have primary responses to vaccination against COVID-19 or influenza.³⁷

Risk-adapted maintenance therapy was evaluated in the FOLL12 trial.³⁸ Over 800 patients with high tumour burden FL who received either R-CHOP or BR were assessed by PET. Those with complete metabolic responses were randomised to four doses of rituximab maintenance if MRD positive by molecular testing for BCL2/IGH, or no further treatment if MRD negative. Those without a complete metabolic response were treated with radio-immunotherapy and then rituximab maintenance. PFS was inferior in those who did not receive maintenance rituximab.

g. Management of Hypogammaglobulinemia:

Exposure to anti-CD20-based therapy increases the risk of hypogammaglobulinemia and

infections, and this risk is further increased by maintenance therapy.³⁹ This is particularly relevant in the COVID-19 era, where recent anti-CD20 use and hypogammaglobulinemia have been associated with poorer outcomes after COVID-19 infection.^{40,41} Low levels of all immunoglobulins may be observed following therapy; however, treatment with intravenous or subcutaneous immunoglobulin (IVIg/SCIg) is only available for low IgG levels and will not impact IgA or IgM. Asymptomatic hypogammaglobulinemia does not require treatment. Immunoglobulin replacement therapy is recommended in symptomatic hypogammaglobulinemia, defined as patients having two or more severe infections within a year.⁴² The typical starting dose is 400–600 mg/kg monthly for IVIg, or 100–200mg/kg weekly for SCIg. There is little evidence regarding the duration of treatment, with some sources suggesting that immunoglobulin replacement therapy may be paused 9–12 months following discontinuation of anti-CD20 therapy, with re-evaluation of IgG and clinical status 3–4 months later.⁴³

h. Vaccine Responsiveness After B Cell Depleting Therapy:

Impaired vaccine responsiveness is a key consideration and should be discussed with patients when offering anti-CD20 therapy. A meta-analysis of 905 patients receiving anti-CD20 therapy demonstrated poor seroconversion rates ranging from 0–25% across all vaccinations studied, including seasonal influenza and pneumococcal vaccinations.⁴⁴ Perry *et al.* demonstrated that patients with lymphoma who had received anti-CD20 therapy within the prior 6 months had a response rate to mRNA COVID-19 vaccines (as measured by antibody titres) of only 7%. In contrast, those who had anti-CD20 therapy >6 months prior had a response rate of 67%, with increasing time from the last anti-CD20 treatment being associated with improved response. Although the B-cell response is impaired, it is possible that COVID-19 vaccination may induce a T-cell responses.⁴⁵ Thus, while anti-CD20 maintenance therapy is generally given in advanced-stage symptomatic FL to prolong PFS, poor vaccine response and subsequent risk of infections must be discussed with the patient, and the patient's individual risk profile should be considered, particularly in the COVID-19 era.

Drug Class	Regimen (trial name)	Setting	Type of Study
Immunomodulators			
• Lenalidomide	Lenalidomide + rituximab (RELEVANCE) Lenalidomide + obinutuzumab	Front-line Frontline	Phase III Phase II
BTK inhibitors			
• Ibrutinib	Ibrutinib + rituximab (PERSPECTIVE)	Front-line	Phase III
• Acalabrutinib	Acalabrutinib +/- rituximab	R/R ≥ 1 prior tx	Phase Ib
• Zanubrutinib	Zanubrutinib	R/R ≥ 1 prior tx	Phase I/II
PI3K inhibitors			
• Idelalisib	Idelalisib	R/R ≥ 1 prior tx	Phase II
• Duvelisib	Duvelisib (DYNAMO)	R/R ≥ 1 prior tx	Phase II
• Copanlisib	Copanlisib (CHRONOS-1)	R/R ≥ 2 prior tx	Phase II
	Copanlisib + rituximab (CHRONOS-3)	R/R ≥ 1 prior tx	Phase III
• Umbralisib	Umbralisib (UNITY-NHL)	R/R ≥ 2 prior tx	Phase IIb
BCL2 inhibitors			
• Venetoclax	Venetoclax + BO (PrECOG-0403) Venetoclax + obinutuzumab (LEVERAGE) Venetoclax + R-CHOP or G-CHOP (CAVALLI) Venetoclax + BR (CONTRALTO) Venetoclax	Front-line Front-line Front-line or 1 prior tx R/R ≥ 1 prior tx R/R	Phase II Phase I/II Phase Ib Phase II Phase I
EZH2 inhibitors			
• Tazemetostat	Tazemetostat Tazemetostat + rituximab (SYMPHONY-1)	R/R ≥ 2 prior tx R/R ≥ 1 prior tx	Phase II Phase III
Monoclonal antibodies			
• Tafasitamab (anti-CD19)	Tafasitamab + lenalidomide + rituximab	R/R ≥ 1 prior tx	Phase III
• Magrolimab (anti-CD47)	Magrolimab + rituximab Magrolimab + venetoclax + obinutuzumab (VENOM)	R/R R/R ≥ 2 prior tx	Phase 1b/II Phase I
Antibody-drug conjugates			
• Polatuzumab vedotin (anti-CD79b)	Polatuzumab vedotin + rituximab	R/R	Phase II
• Loncastuximab tesirine (anti-CD19)	Polatuzumab vedotin + lenalidomide + obinutuzumab Loncastuximab tesirine Loncastuximab tesirine + rituximab	R/R ≥ 1 prior tx R/R R/R	Phase Ib/II Phase I Phase II
Bispecific antibodies			
• CD19targeted	Blinatumomab	R/R ≥ 1 prior tx	Phase I
• CD20-targeted	Mosunetuzumab + polatuzumab vedotin Mosunetuzumab Glofitamab +/- obinutuzumab Epcoritamab + rituximab +/- lenalidomide (EPCORE NHL-2) Odronektamab (ELM-1)	Front-line R/R ≥ 2 prior tx R/R ≥ 1 prior tx Front-line R/R ≥ 1 prior tx	Phase II Phase II Phase I Phase Ib/II Phase I
CAR-T cell therapy	Axicabtagene ciloleucel (ZUMA-5) Tisagenlecleucel (ELARA) Lisocabtagene maraleucel (TRANSCEND)	R/R ≥ 2 prior tx R/R ≥ 2 prior tx R/R	Phase II Phase II Phase II
Immune checkpoint inhibitors	Pembrolizumab + rituximab	R/R ≥ 1 prior tx	Phase II

Table 3. Promising future treatments; clinical trials either completed or ongoing in the front-line setting, and selected studies in the relapsed/refractory setting; courtesy of *Samantha Hershenfeld, MD, FRCP, Jennifer Teichman, MD, FRCP, and Neil L. Berinstein, MD, FRCP*.

Abbreviations: **BO:** bendamustine + obinutuzumab; **BR:** bendamustine + rituximab; **BTK:** Bruton's tyrosine kinase; **G-CHOP:** obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisone; **PI3K:** phosphoinositide 3-kinase; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **R/R:** relapsed/refractory; tx treatments.^{42, 43}

Conclusion

While follicular lymphoma is an indolent lymphoma with excellent long-term survival, the majority of patients will require multiple lines of treatment in their disease course. Prognostic models such as the FLIPI or FLIPI-2 may identify those with favourable or unfavourable prognosis and those with very unfavourable outcome are identified by POD24. BR with maintenance rituximab is the standard of care for symptomatic patients with advanced stage disease, but an individualized treatment approach should include an assessment of infection risk. For frail patients unable to tolerate bendamustine, rituximab with or without lenalidomide is an option. Novel agents including EZH2 inhibitors and BiTEs may have a front-line role in the future, but randomized phase III data are currently lacking. Long-term follow up of patients treated with frontline therapy should include monitoring for signs and symptoms of histologic transformation and for the complications of hypogammaglobulinemia. Patients on treatment with anti-CD20 monoclonals are unlikely to mount protective immune responses to antimicrobial vaccines for at least 6 months after the last treatment dose.

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Burkitt Lymphoma: The Curable Challenge

Adam J. Olszewski, MD

Introduction

Among the multiple subtypes of non-Hodgkin lymphoma, Burkitt lymphoma (BL) holds a unique position as the most aggressive mature B-cell malignancy. Named after the British physician who first described rapidly growing jaw and abdominal tumours in Ugandan children in 1958, BL is now understood to be a highly proliferative lymphoma arising from B-cells in the dark-zone germinal centre. BL is driven by the hallmark genomic lesion (*IG::MYC* rearrangement) and occurs in specific epidemiologic and clinical contexts.¹⁻⁴

Historically, BL was classified as follows: “endemic” (common in the equatorial strip, associated with Epstein-Barr virus [EBV] and malaria infections, and predominantly pediatric), “immunodeficiency-associated” (in individuals with HIV infection or a history of solid organ transplantation), or “sporadic”—which includes 80% of cases observed in Canada and the United States (US). However, the current World Health Organization classification of lymphomas has discounted those descriptive terms and instead it recommends describing BL according to the

presence or absence of EBV in the tumour, which provides more biological relevance.⁵

BL has an age-standardized incidence of 4 per million person-years, with a median age at diagnosis of 40 years, and an incidence three times higher in men than in women.⁶ The incidence shows one peak in childhood, another around the age of 40 for men (partly due to the association with HIV), then it steadily increases after the age of 60 years, reflecting immune senescence.

BL often presents with clinical emergencies, which highlights the importance of promptly recognizing its symptoms for a rapid diagnostic workup and therapy. Patients with BL present with rapidly growing nodal disease, often disseminated to extranodal organs. Approximately 20% of BL cases may resemble acute lymphoblastic leukemia, with extensive bone marrow, blood, and frequent central nervous system (CNS) involvement. Serum lactate dehydrogenase (LDH) is typically elevated, and some patients may develop spontaneous tumour lysis syndrome (TLS) with life-threatening hyperkalemia, hyperuricemia, and renal failure, even before therapy starts. In a recent study that

included 641 US adults with BL, 78% had stage 3 or 4 disease, 43% had ≥ 2 extranodal sites of involvement, 35% had disease in the bone marrow, and 19% showed infiltration of the CNS (**Fig. 1A**).⁷ Curiously, approximately 15% of patients present with only a single, large tumour arising from the ileocecal intestine that may involve regional lymph nodes, which raises a suspicion of colon cancer. In these patients, initial surgery may be performed due to emergent bowel obstruction or perforation, with an occasional complete resection of the BL tumour. The ileocecal location, together with the other known primary tumour locations in the jaw or the breasts of lactating women, hypothetically reflect genomic errors occurring when B-cells undergo immunoglobulin class switching to IgA in those organs.²

The initial medical workup of a patient with suspected BL is often undertaken in the inpatient setting owing to the rapid and relentless increase in the lymphoma burden. Early use of corticosteroids after or even before a diagnostic biopsy can be life-saving; however, this treatment requires close clinical and laboratory monitoring due to the risk of TLS. Diagnostic procedures typically involve a biopsy of the nodal or extranodal mass, although examination of the bone marrow or even peripheral blood or cerebrospinal fluid (by flow cytometry) may yield the diagnosis. The presence of vacuolated lymphoma cells with a characteristic immunophenotype and confirmatory *MYC* rearrangement suggests BL. An additional laboratory workup should include an assessment of blood counts, kidney and liver function, LDH, and serologies for hepatitis B, C, and HIV. Radiologic staging often relies on imaging with computed tomography or, when feasible, positron emission tomography (PET), with further evaluation of possible involvement of the blood/bone marrow, and mandatory sampling of the cerebrospinal fluid to rule out CNS invasion.

The histopathology of BL is distinct, revealing a dense, monotonous “blue cell” infiltrate consisting of medium-sized B-cells with extensive mitotic activity, and scattered tingible body macrophages that create the characteristic “starry sky” appearance on a low magnification view. BL cells strongly express CD10, CD19, CD20, and B-cell lymphoma 6 (*BCL6*), affirming their germinal centre B-cell origin. Conversely, they should not exhibit B-cell lymphoma 2 (*BCL2*), CD5, or terminal deoxynucleotidyl transferase (TdT), which facilitates rapid differentiation from B-lymphoblastic lymphoma/leukemia, or

blastoid mantle cell lymphoma. Considering the morphologic and immunophenotypic overlaps between BL and other high-grade B-cell lymphomas (HGBL), diagnostic confirmation of the *MYC* rearrangement through chromosome analysis or fluorescent *in situ* hybridization (FISH) is important. Approximately 80% of BL tumours show the typical t(8;14)(q24;q32) *IGH::MYC* rearrangement, while most others involve translocations to light-chain immunoglobulin loci.³ A lack of other karyotypic abnormalities, especially the absence of concurrent *BCL2* or *BCL6* translocations or copy number alterations, differentiates BL from HGBL with *MYC* and *BCL2* rearrangements or HGBL, not otherwise specified. Some cases of BL may test negative for *MYC* translocation, requiring additional workup to rule out rare entities such as HGBL with 11q aberration. Sequencing studies have identified recurrent somatic mutations in BL, including *TCF3*, *ID3*, *TP53*, *DDX41*, *CCND3*, or *FOXO1*, which contribute to our understanding of the highly proliferative nature of BL, its dependence on specific intracellular signals, and the role of EBV infection in lymphomagenesis.^{2,3,8}

Unfortunately, the advances in molecular biology have not yet been translated to prognostic assessments or treatment decisions, which continue to rely on clinical features. A comprehensive international analysis identified four prognostic factors at diagnosis of BL (age >40 years, poor performance status, CNS involvement, and LDH >3x upper limit of normal). These factors provide clinical prognostic stratification for adults with BL. For instance, long-term progression-free survival ranges from 92% for those with no risk factors to only 53% for those with two or more factors.⁹ Importantly, HIV infection does not appear to significantly compromise outcomes, possibly due to BL occurring in patients with less advanced immunodeficiency (median CD4 T-cell count of approximately 200 per mm³). Many patients require initial stabilization due to TLS or organ impairment, including a cautious “debulking” pre-phase using corticosteroids (e.g., dexamethasone 20 mg daily for 5 days) with or without fractionated cyclophosphamide (e.g., 200 mg/m² for 5 days) to facilitate the diagnostic workup and therapy preparation.

Pediatric hematologists typically treat children and adolescents with BL using short-duration, dose-intensive chemotherapy regimens that are designed for aggressive mature

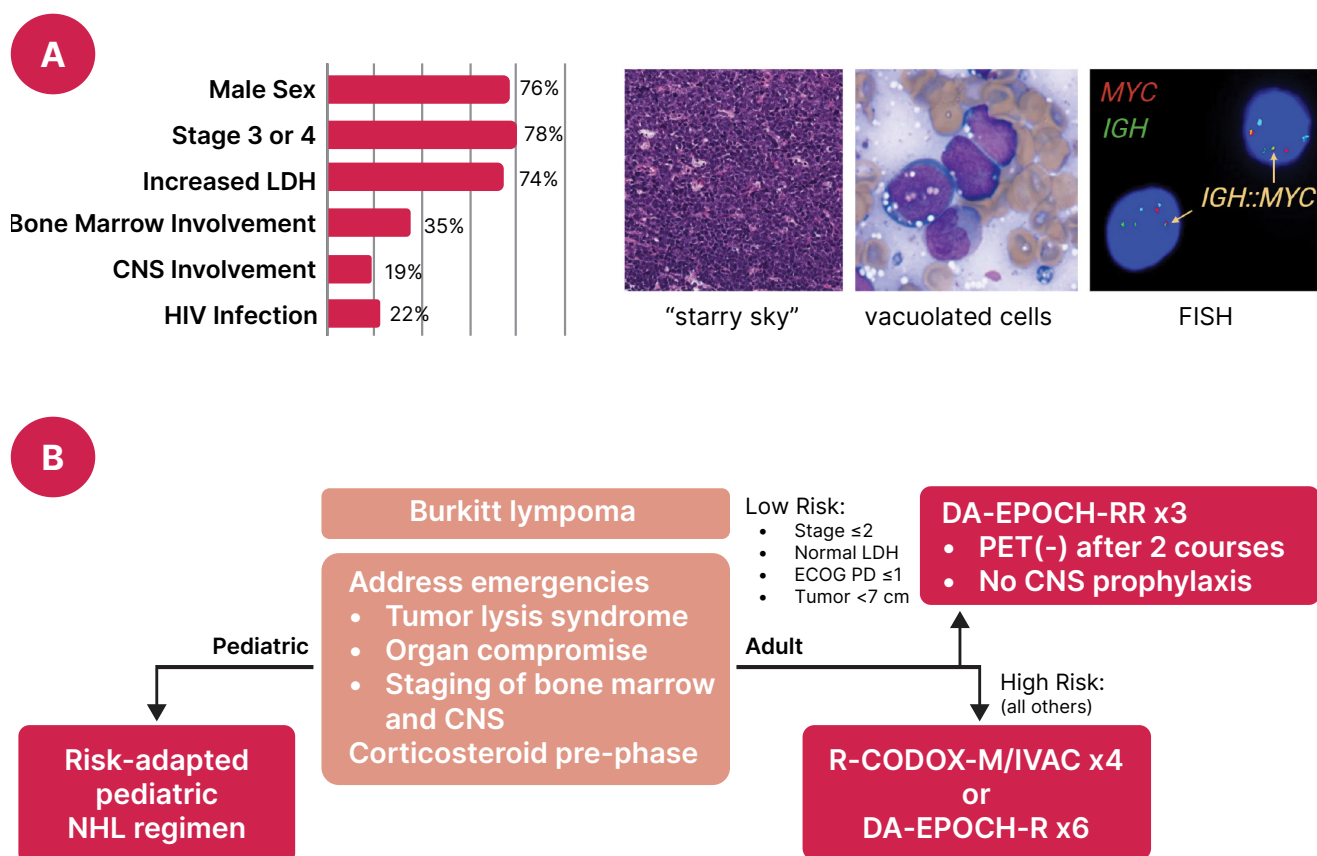


Figure 1. Clinico-pathologic characteristics **(A)** and treatment algorithm **(B)** for Burkitt lymphoma; figure created with BioRender.com.

Abbreviations: CNS: central nervous system; DA-EPOCH R: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; ECOG PS: Eastern Cooperative Oncology Group; FISH: fluorescent in situ hybridization; LDH: lactate dehydrogenase; NHL: non-Hodgkin lymphomas; PET: positron emission tomography; R-CODOX-M/IVAC: rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate, alternating with ifosfamide, etoposide, and cytarabine

B-cell lymphomas, regardless of histologic subtype.¹⁰ These regimens, incorporating rituximab and CNS-penetrant agents, are risk-adapted, are based on disease burden (stage, resection status, bone marrow and CNS involvement) and result in long-term event-free survival for 94% of children, even with high-risk disease.¹¹ For adult patients, curative therapy also involves short, dose-intense regimens. However, these regimens are associated with higher toxicity and less favourable outcomes in adults than in children with BL (**Fig. 1B**).^{3,4,12} Standard-intensity protocols such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) may be inadequate and often

lead to chemoresistance and early progression of BL. In North America, 3 immunochemotherapy regimens are commonly used, with the choice depending on local expertise. These regimens include R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate, alternating with ifosfamide, etoposide, and cytarabine),¹³⁻¹⁵ R-hyperCVAD/MA (rituximab, hyper-fractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone, alternating with methotrexate and cytarabine),¹⁶ and DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab).^{15,17,18} Different but conceptually similar protocols are used in other

countries, sharing the overall plan of dose intensity and include rituximab and CNS-directed intrathecal and/or systemic therapy, and no maintenance therapy. Treatment can be stratified according to disease burden, being significantly shortened for patients with low-risk features, which are variably defined as a single or localized stage 1 or 2 tumour <7 cm in size, with normal LDH levels and a good performance status. The R-CODOX-M schema allows for the treatment of low-risk BL with 3 courses of R-CODOX-M (omitting the IVAC modules),¹³ while the low-risk DA-EPOCH-R schema (applicable if a complete response is confirmed by a PET scan after the initial 2 courses) includes a total of 3 courses of chemotherapy with double-dosing of rituximab and without any intrathecal CNS prophylaxis.^{17,18} Prospective comparative data between various protocols are limited; however, observational studies suggest no difference in outcomes,⁷ and one randomized trial showed no survival difference between the R-CODOX-M/IVAC and DA-EPOCH-R protocols for high-risk BL, with 2-year progression-free survival of 76% and 70%, respectively. However, the trial was underpowered due to incomplete accrual.¹⁵ Some observational studies show higher treatment-related mortality with the R-hyperCVAD/MA protocol, which requires prolonged, intensive therapy.⁷ The DA-EPOCH-R protocol offers significant practical advantages due to its outpatient administration and lower toxicity, thus providing effective curative therapy for patients aged over 60 years, and those who are unable to tolerate more intensive regimens. However, this protocol lacks high-dose CNS-penetrant agents, thus requiring meticulous and intensive CNS prophylaxis. However, this protocol may be insufficient in a setting of CNS involvement, in which many clinicians favour regimens that contain high-dose methotrexate and cytarabine.

Patients with BL undergoing dose-intense therapy require expert supportive care to ensure safe and uninterrupted treatment delivery. The initial cycle of chemotherapy is critical due to frequent organ compromise at diagnosis, the risk of tumour lysis, bowel perforation, profound cytopenia when the bone marrow is involved, and a high risk of potentially fatal sepsis. Supportive measures for patients with BL should always include the use of granulocyte growth factor (regardless of age), antibacterial, antiviral, and *Pneumocystis jirovecii* pneumonia prophylaxis. HIV-positive patients can receive standard intensive protocols such as R-CODOX-M/IVAC

or DA-EPOCH-R; however, they require attention regarding the risk of opportunistic infections and interactions between chemotherapy and antiviral agents. BL is best treated in centres providing expertise in management, including familiarity with chemotherapy protocols, established procedures for timely intrathecal chemotherapy delivery, and resources for transfusions and other medical and psychosocial support during intensive and partly inpatient therapy. Successful initial therapy delivery is essential owing to the “all or nothing” effect. Most patients completing treatment without major complications or interruptions are cured of BL, and recurrences beyond 1 year after therapy are rare. In contrast, patients not achieving a complete response or experiencing a recurrence, often soon after the end of initial therapy, frequently have chemoresistant disease, which may not respond to salvage therapy. The traditional pathway of reinduction using non-cross-resistant chemotherapy followed by consolidative (autologous or allogeneic) stem cell transplantation rarely leads to long-term survival, either in the pediatric or adult setting. Although several novel strategies have recently been developed for diffuse large B-cell lymphoma (DLBCL), including antibody-drug conjugates such as polatuzumab vedotin or loncastuximab tesirine, chimeric antigen receptor T-cells (CAR T-cells), and CD20xCD3-targeting bispecific antibodies, their efficacy in BL remains to be evaluated. One observational study suggests that autologous CAR T-cells are associated with less favourable outcomes in BL than in DLBCL, with only 31% of patients sustaining a complete response after 6 months of therapy, with a median progression-free survival of 4 months.¹⁹

Conclusion

Current research on BL is focused on incorporating novel immunotherapies into first-line treatment. Major areas of need include developing treatments applicable to older patients with comorbidities or designing management strategies for countries with limited medical resources, in which delivery of multiagent chemotherapy is challenging. The recently established BL Network (<https://www.burkitt-lymphoma.org/>) aims to bring together international researchers dedicated to improving outcomes of patients with this rare cancer.

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Follicular Non-Hodgkin Lymphoma: First Relapse and Beyond

Mary-Margaret Keating, MD

Introduction

Follicular lymphoma (FL) is the most common indolent subtype of non-Hodgkin Lymphoma (NHL) and the second most common type of lymphoma overall.^{1,2} In Canada the age-standardized incidence of FL is 38.3 cases per million individuals per year with mean age at diagnosis of 60 and similar incidence in men and women.³ Follicular lymphoma is treatable but not curable with systemic therapy yet it maintains a median overall survival (OS) of approximately 20 years.⁴ Historically, this long median survival has been maintained through periods of watchful waiting and subsequent treatment with chemoimmunotherapy when the disease burden becomes symptomatic. Serial relapses with progressively shorter remissions and more resistant disease is the usual natural history for FL.^{5,6} The management of relapsed FL remains controversial and the decision on next line of therapy is a rapidly evolving area, with the old standard repetition of chemoimmunotherapy being contested by new targeted therapies. There remains a challenge for Canadian patients to access these novel therapies outside of clinical trials and access programs. This review

will present a treatment approach for relapsed FL taking into consideration Canadian funding patterns, in addition to reviewing the novel drugs with the highest level and most mature evidence to date.

First-line Therapy

Outside of specific populations where radiotherapy or single agent rituximab may be appropriate, front-line therapy for symptomatic FL in Canada remains standardized with most centres using chemoimmunotherapy with bendamustine and rituximab (BR), based on the safety and efficacy demonstrated in the BRIGHT and StIL trials.⁷⁻¹⁰ The option for a subsequent 2 years of maintenance rituximab is more controversial with concerns around prolonged B-cell dysfunction, infectious risk and the long-term follow up from the PRIMA study showing improved progression-free survival (PFS) but not overall survival (OS).¹¹ Nevertheless, many centres, ours included, offer this therapy as the median PFS of 10.5 years leads to a prolonged treatment-free period for patients and caregivers vs the 4.1 year PFS without maintenance.¹¹ These initial years of watchful waiting along with the typical long

front-line remission constitute a major duration of the median OS seen with follicular lymphoma.

Duration of First Remission

As clinicians, we start to worry when a FL patient relapses aggressively and/or early. The average first remission for FL is 4–10 years and patients who relapse well before the median are said to have an early relapse also known as “progression of disease within 24 months” (POD24)^{5,12,13} Multiple studies have found inferior outcomes with this group with OS as low as 38–50% at 2 to 5 years of follow-up which is quite dismal when compared with patients without POD24 who have a 5-year OS of 90%.^{5,12,13} In addition to the survival concern for patients with POD24, a Canadian retrospective study from 2019 found that 76% of patients with FL post-initial BR chemoimmunotherapy with POD24 have transformed disease.¹² Histologic large cell transformation needs to be considered for any relapsing patient with FL given that there is a 1–2% yearly risk of transformation and 15% of patients will experience transformation during their disease course.¹⁴

Options at First Relapse

Retreatment with chemoimmunotherapy

In Canada, first relapse of FL has generally been treated with rituximab-based chemoimmunotherapy, especially for those patients who have had a reasonable remission with first-line therapy. A retrospective Ontario patient cohort (2005–2013) demonstrated that 64% of FL patients received R-CVP (cyclophosphamide, vincristine, prednisone) as first-line treatment; subsequently second-line therapy was monotherapy chemo in 40% and BR in 32%.¹⁵ The effectiveness of BR in relapsed but not refractory FL has been demonstrated in 2 Phase 2 clinical studies that yielded similar results with an overall response rate (ORR) of 90–92% and median PFS of 23–24 months.^{16–18} In comparison, use of single agent bendamustine in a cohort of relapsed indolent NHLs yielded an ORR of 76% with a median duration of response (DOR) of 10 months.¹⁸ Taking into consideration other local funded options or clinical trials, chemoimmunotherapy may be the best option available for patients who have an average or better first remission.

For the subgroup of approximately 20% relapsed or refractory (RR) FL with POD24, retreatment with the original R-chemotherapy is less appealing. Several studies have shown inferior responses to bendamustine in the R refractory population with ORRs of 75–77% and median DOR of 6.7–9.2 months.^{19,20} The GADOLIN study enrolled patients who were rituximab refractory, with POD24, and randomized to receive obinutuzumab (O), a second-generation anti-CD20 monoclonal antibody, with bendamustine (B) or B monotherapy. If there was no progression of disease, patients in the OB arm subsequently received maintenance O.^{21,22} At a median follow-up of 32.6 months in the OB group and 19.3 months in the B group, the median PFS was 25.3 months for OB and 14 months for B monotherapy (P<0.001). Additionally, in the combination group an OS advantage was seen with median OS not evaluable vs 53.9 months in the B monotherapy group.^{21,22} Although a novel therapy or clinical trial would be favoured in this population of patients, the GADOLIN results show that repeat chemoimmunotherapy in a POD24 population is a reasonable option and it is reimbursed in Canada.

Rituximab + lenalidomide

The combination of rituximab and lenalidomide (R2) was introduced as an alternate approach for treatment of relapsed FL and is reimbursed in some Canadian provinces based on the AUGMENT trial, published in 2019.²³ This Phase 3 trial randomized patients with RR FL and marginal zone lymphoma with ≥1 previous lines of therapy (>50% had 1 prior line only) to receive with R2 vs R monotherapy.²³ The primary outcome was met for R2 which showed a median PFS assessed by an independent review committee (IRC) of 39.4 months vs 14.1 months for R monotherapy.²³ This PFS benefit was maintained in higher risk populations such as refractory to last line of treatment and time from last therapy, highlighting that this may be a good option for POD24 patients. Additionally, R2 had a favourable median DOR of 39.4 months vs 14.1 months.²³ It is important to consider the side effects of the R2 arm which, not surprisingly, had higher rates of skin reactions, infection, and Grade 3–4 neutropenia requiring growth factor use and dose reductions. If R2 is reimbursed it is a nice alternative or addition to repeating chemoimmunotherapy in RR FL.

Lenalidomide + obinutuzumab

Also in 2019, the single arm GALEN Phase 2 trial adopted a different approach and combined lenalidomide (L) with obinutuzumab for 6 cycles followed by 1 year of maintenance L and 2 years of MO in 86 patients with relapsed FL with ≥ 1 prior lines of treatment.²⁴ The primary endpoint was ORR at end of induction which was reported at 79.1% (95% CI, 68.9-87.1); the 2-year PFS and DOR were 64% and 69.6% respectively.²⁴ Currently this is not a protocol that is conventionally reimbursed in Canada.

Options at Second Relapse

When a patient with FL relapses a second time, similar considerations regarding transformation, duration of remission, prior lines of therapy and patient fitness should be reviewed. The next best option may be a choice that has been discussed above, clinical trial or radiation treatment if only one area of disease is a concern. However, the time to consider an autologous stem cell transplant (ASCT) is either at first or second relapse if this is a viable option for the patient. This is a controversial area without strong data and inherent difficulty in identifying patients who may benefit from this type of intensive therapy.

Autologous Stem Cell Transplant

Although there are a number of novel therapies for FL, thus far the PFS remain short with many patients relapsing by 2–3 years.^{23,25} ASCT is a traditional therapeutic option for RR FL with some older prospective studies suggesting a benefit for a small subset of patients who achieve long-term PFS.^{26,27} There is the background concern of early and late adverse events from this high-dose therapy. The CUP trial showed improved OS and PFS for ASCT over chemotherapy alone but was conducted in the pre-rituximab era.²⁷ There are a number of publications reporting prolonged PFS but they are all retrospective and therefore have inherent bias.^{28–31} $P < 0.001$ Recently published retrospective Canadian data from a single centre of 162 patients with RR FL undergoing ASCT reported a 12-year PFS of 51% and OS of 69%.³² They reported no relapses starting at 9 years after ASCT. The best outcomes were seen in patients undergoing ASCT as a second-line treatment and who did not have POD24.³² Outcomes with ASCT were superior for patients at first or second relapse with

a 12-year time to progression of 61% vs 34% for patients at third or later relapse. Unfortunately, there is a lack of modern prospective trials comparing ASCT to standard of care to make a strong recommendation around this therapy. It is reasonable to consider ASCT in a younger, fit patient who is chemotherapy-sensitive in earlier rather than late relapse, especially if there are limited other funded or trial-related novel options.

Options for Third-line Relapse and Beyond

Several novel agents have been studied and approved for the treatment of multiply relapsed FL, none of which are currently reimbursed in Canada. A summary of the drugs and cellular therapy that have the most mature data, also summarized in **Table 1**.

Mosunetumumab

Mosunetumumab is a bispecific T-cell engaging (BiTE) antibody against CD20 on FL cells and CD3 on T cells that received approval in 2022 in both the United States and Europe. The licensing study was a single arm, Phase 2, which enrolled 90 patients with ≥ 2 prior lines of therapy, including an alkylator and anti-CD20.³³ Patients were treated for at least 8 cycles but if partial response or stable disease, it was continued for up to 17 cycles. The primary endpoint was a complete response (CR) rate determined by an IRC which was reported in 60%.³³ The 3-year follow-up data was recently presented at the American Society of Hematology meeting in 2023.³⁴ With a median follow-up time of 37.4 months the median PFS was 24 months and for patients who achieved a CR the median DOR was 35.9 months.³³ Overall, mosunetumumab is showing promising activity but longer term follow-up is needed.³³ Other BiTE therapies have been studied in FL but are not yet approved. A comprehensive review has been published recently.³⁵

Tazemetostat

Tazemetostat is a first-in-class oral EZH2 inhibitor that received accelerated FDA approval in 2020 for adult patients with relapsed or refractory (R/R) FL whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received ≥ 2 prior lines of systemic therapy, and for adult patients with R/R FL who have no satisfactory alternative treatment options. Health Canada approval has not yet been pursued.

Novel Drug	Trial	Phase	N	Prior lines	ORR	CR	Median PFS (months)
Lenalidomide + rituximab ²³	AUGMENT	3	147 vs 148	≥1	80% vs 55%	35% vs 20%	30 vs 14
Mosunetuzumab ³⁴ mosunetuzumab demonstrated a high complete response (CR)	NCT02500407	2	90	≥2	80%	60%	24
Tazemetostat ³⁸	NCT05467943	2	45 ^{mut} 54 ^{wt}	≥2	69% ^{mut} 35% ^{wt}	13% ^{mut} 4% ^{wt}	10.9 ^{mut} 13 ^{wt}
Zanibrutinib + obinutuzumab ⁴⁴	ROSEWOOD NCT03332017	2	217	≥2	69%	39%	28
Axi-cel ⁴⁹	ZUMA-5 NCT03105336	2	127 FL 31 MZL	≥2	94% FL	79% FL	3y PFS 54%
Tisa-cel ⁵⁰	ELARA NCT03568461	2	94	≥2	86%	68%	2y PFS 57%

Table 1. Novel drugs with the most mature efficacy data for RR FL; courtesy of Mary-Margaret Keating, MD.

Abbreviations: N: number; ORR: overall response rate; CR: complete response; PFS: progression-free survival; mut: EZH2 mutated; wt: EZH2 wildtype; FL: follicular lymphoma; MZL: marginal zone lymphoma

EZH2 is a histone methyltransferase responsible for formation of the germinal center and limiting B-cell proliferation.^{36,37} Activating mutations of EZH2 are found in approximately 20% of patients with FL.^{36,37} The Phase 2 registration trial enrolled 99 patients with RR FL, 45 with mutated EZH2 and 54 with wild type.³⁸ The ORR for the mutated group was 69% and 35% for the wild type patients. The median DOR was similar between mutated vs wild type groups at 10.9 months vs 13 months which called into question if mutational testing should be required to use this therapy.³⁸ This medication was well tolerated with a low number of patients needing a dose delay or reduction, potentially making it more appealing for an older and or more frail population.³⁸

Zanubrutinib

Bruton tyrosine kinase inhibitors (BTKi) interfere with a key pathway in B-cell lymphomas and have been successfully introduced as effective therapy for several types of RR non-Hodgkin lymphoma.^{39,40} Results from follicular

lymphoma studies using ibrutinib, a first generation BTKi, either as a single agent or in combination with rituximab, have yielded disappointing results.^{41–43} More recently, the ROSEWOOD study has shown encouraging results using the second generation BTKi zanibrutinib in combination with obinutuzumab.¹² This randomized Phase 2 study of 217 patients with R/R FL with ≥2 prior lines of therapy (including anti-CD20 and alkylator) showed an ORR and median PFS of 69% and 28 months for ZO vs 46% and 10.4 months for O monotherapy.⁴⁴ The estimated 2-year OS was 77% vs 71% favouring ZO therapy.¹² A Phase 3 study is underway using zanubrutinib along with an anti-CD20 vs R2 in patients with ≥1 prior lines of therapy with RR FL and MZL (MAHOGANY). This may further clarify the role of BTKi's in the treatment of FL.

PI3K Inhibitors

There are currently no PI3K inhibitors on the market for RR FL. Most recently in November 2023 copanlisib was withdrawn from

the U.S. market.^{45,46} These medications (idelalisib, duvelisib, umbralisib) all had conditional FDA approval for RR FL based on initial early-phase studies but subsequent data has revealed inadequate benefit to side effect ratio.⁴⁵

CAR-T

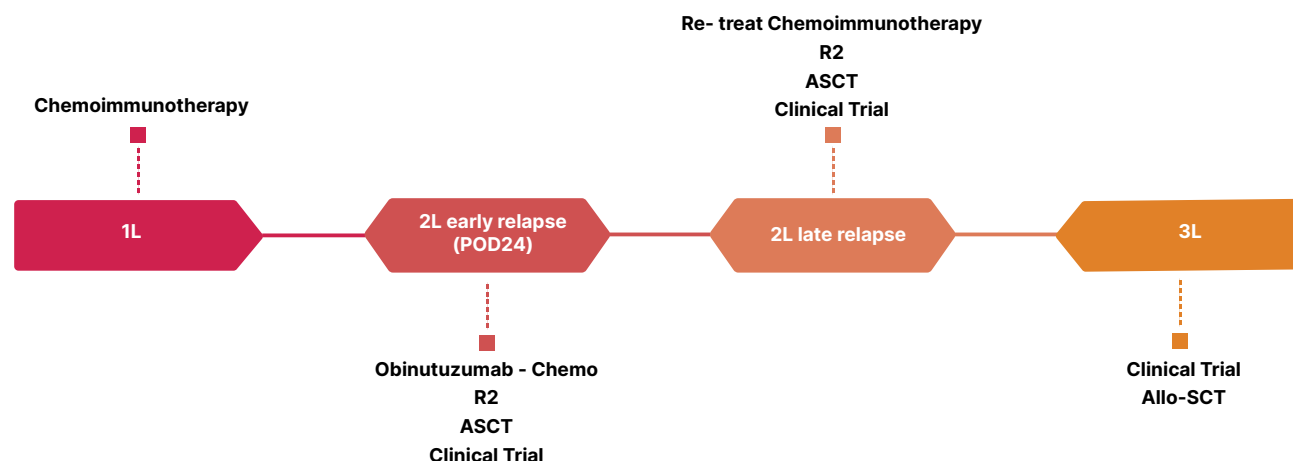
Two chimeric antigen receptor (CAR) T-cell therapies are Health Canada approved with final funding decisions having been rendered for RR FL after ≥ 2 prior lines of therapy: axicabtagene ciloleucel (axi-cel), a CD28-based agent and tisagenlecleucel (tisa-cel) a 4-1BB based CAR T product.^{47,48} CADTH recommends that Yescarta be reimbursed by public drug plans for the treatment of adult patients with R/R FL who have grade 1, 2, or 3a FL and whose disease has returned following second-line treatment or later lines of treatments. Similarly, CADTH also recommends that Kymriah be reimbursed by public drug plans for the treatment of adults with R/R FL for patients who have not already received a CAR T-cell therapy, are in relatively good health, and the cost of Kymriah is reduced. Overall, the Phase 2 ZUMA-5 study demonstrated that at median follow up of 40.5 months, axi-cel had an ORR of 90%, CR rate of 75%, and 3-year PFS of 54%.⁴⁹ The tisa-cel phase II ELARA trial had an ORR of 86%, CR 68%, and 2-year PFS of 57%.⁵⁰ These patients all had received 3–4 prior lines of therapy. It was encouraging that patients with recent POD24 did equally well with these CAR-T products. A comprehensive review of CAR-T cell therapy for RR FL is nicely covered in a past issue of Canadian Hematology Today.³⁵

Allo SCT

Utilizing a graft-versus-lymphoma effect with a nonmyeloablative or reduced intensity allogeneic stem cell transplant (alloSCT) is appealing with the possibility of cure for multiply relapsed FL. However, concerns remain around non-relapsed mortality (NRM).⁵¹ The level evidence available makes recommending choosing allo vs ASCT challenging, as most data sets are retrospective and subject to bias. A number of smaller retrospective studies have reported potential cure or long-term disease control in 40–60% of patients with RR FL but with an NRM of 10–30%.^{51,52} Overall, alloSCT is a controversial but potentially curative treatment option for younger, more fit patients with multiply relapsed FL who have exhausted other treatment options. With newer therapies on the horizon the role of ASCT and alloSCT is likely to lessen.

Summary

The treatment landscape for RR FL is rapidly evolving with novel agents attempting to overcome the barriers of POD24 and chemoimmunotherapy resistant disease. Although access to these newer options is lacking in Canada, hopefully with longer-term and more robust data they will become part of standard care (**Figure 1**). Continued support and greater patient access to clinical trials will be important in the coming years so that they can benefit from these innovative therapies earlier.



***Clinical trial to access: BiTEs, Tazemetostat, 2nd gen BTKi, CAR-T**

Figure 1. A potential Canadian approach to the treatment of RR FL; *courtesy of Mary-Margaret Keating, MD.*

Abbreviations: 1L: first line of therapy; 2L: second line of therapy; 3: third line of therapy; R2: lenalidomide + rituximab; ASCT: autologous stem cell transplant

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Dr. Lee received an MD from the University of British Columbia and completed internal medicine and hematology residency at the University of Toronto. She completed a fellowship in the Acute Leukemia and Myeloproliferative Neoplasms Program at the Princess Margaret Cancer Centre in Toronto followed by a MSc degree in Epidemiology and Clinical Research at Stanford University. She is currently a hematologist at St. Michael's Hospital in Toronto and an Assistant Professor at the University of Toronto. She helped establish St. Michael's Hospital as the only Canadian centre of excellence in mast cell disorders with the American Initiative in Mast Cell Diseases and is currently the primary investigator of the program at St. Michael's Hospital.

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Systemic Mastocytosis: Diagnosis and Management in 2024

Stephanie Lee, MD, MSc, FRCPC

Abstract

Mastocytosis is a group of clonal disorders characterized by an accumulation of neoplastic mast cells (MCs) in one or more organ systems. The clinical presentation of mastocytosis is heterogenous as are the clinical outcomes. For example, some variants are associated with near normal life expectancy, while others are amongst the most aggressive known malignancies. Mastocytosis can occur in both pediatric and adult populations and can be classified into three major groups: systemic mastocytosis (SM), cutaneous mastocytosis (CM), and localized mast cell sarcoma. This review will focus on SM in adults with the aim of providing a general overview of the (1) pathophysiology, (2) diagnostic approach, and (3) current treatment landscape in Canada.

Epidemiology

SM is a rare neoplasm. The incidence and prevalence of SM are poorly characterized due to its rarity, but estimated at 1/100 000 and 1/10 000, respectively.^{1,2} While evidence suggests

that SM has a higher prevalence in women, advanced disease appears to be more common in men.^{2,3} The mean age at diagnosis occurs in the 5th to 7th decade of life and the median time to diagnosis from symptom onset is estimated to be approximately 3 years.³

Pathophysiology of Systemic Mastocytosis

Human MCs originate from CD34⁺ pluripotent progenitor cells in the bone marrow.⁴ Mature MCs in their normal state have a well described role as effector cells in immediate-type hypersensitivity reactions.⁵⁻⁷ A critical part of the differentiation, growth, and survival of MCs is the interaction of stem cell factor (SCF) with KIT, a tyrosine-kinase receptor located on the surface of MCs. Mutations in the *KIT* gene are present in approximately >90% of patients with SM and by far the most common mutation among them is the *KIT* p.D816V mutation. This mutation induces a constitutive SCF-independent hyperactivation state of the KIT receptor, which contributes to

an over production of MCs, an amplification of MC mediator release, and the accumulation of MCs in organs such as the bone marrow, skin, liver, spleen, lymph nodes, and gastrointestinal (GI) tract.^{8–11}

Clinical Presentation of Systemic Mastocytosis

Allergy and Mediator Symptoms

Many patients with SM, especially those with non-advanced disease, often present with symptoms related to excessive MC activation. The release of mediators from MCs affects multiple organs, and patients can exhibit a variety of symptoms including cutaneous (e.g., flushing, pruritus, hives), cardiovascular (e.g., dizziness, syncope), GI (e.g., diarrhea, nausea, vomiting, abdominal pain, gastroesophageal reflux disease), musculoskeletal (e.g., bone pain), and neuropsychiatric symptoms (e.g., brain fog, anxiety, depression), fatigue, and anaphylaxis. Common triggers for MC activation include exercise, changes in temperature, physical and emotional stress, food, alcohol, medications (e.g., nonsteroidal anti-inflammatory agents, anesthetic agents, opioids), radiocontrast agents, invasive procedures, and venoms.⁷ In SM, the rate of anaphylaxis is significantly higher than that of the general population, and is estimated to occur in approximately 20–50% of adult patients with SM.^{12,13} An important trigger to be aware of is hymenoptera venom (e.g. yellowjacket wasp, paper wasp, honeybee, fire ant). Anaphylaxis from hymenoptera venom is estimated to account for up to one third of all cases of anaphylaxis, is a risk factor for severe recurrent anaphylaxis, and is often the presenting symptom in patients with indolent SM.^{14–18}

Bone

Bone abnormalities are common clinical features in patients with SM. Osteoporosis/osteopenia occurs in approximately 20–40% of patients with indolent SM and the prevalence of these bone abnormalities tends to be higher in men. Patients can also present with osteosclerosis, which tends to be more common in advanced stages of the disease, as well as lytic bone lesions in the axial and appendicular skeleton that can mimic skeletal metastasis.^{19–23}

Organ Infiltration

Infiltration of MCs into the skin is a common finding in SM, especially in non-advanced stages of the disease.²⁴ The most common skin manifestation of SM is maculopapular CM (previously referred to as urticaria pigmentosa), which is characterized by small, round, brown/red monomorphic lesions and Darier's sign is usually evident in these cases.²⁴ In adult-onset mastocytosis in the skin, the likelihood of having SM is extremely high (up to 97% in some studies).²⁵ Patients with SM can present with lymphadenopathy and splenomegaly due to MC and/or eosinophil infiltration along with possible extramedullary hematopoiesis. Progressive lymphadenopathy and significant splenomegaly are more commonly observed in advanced stages of the disease.⁷ MC infiltration of the liver is common and can occur with liver dysfunction, ascites, and portal hypertension, all of which reflect advanced SM. Patients with SM can present with malabsorption and weight loss, which is also suggestive of advanced stages of the disease.⁷

Establishing the Diagnosis

Initial Workup:

International guidelines recommend that patients be referred to centres with experience in the diagnosis and management of SM.^{26–28} The work up for SM includes a thorough history and physical exam, a complete blood count with differential and smear, a comprehensive metabolic panel, liver function tests, albumin, basal serum tryptase level, and imaging to evaluate for hepatosplenomegaly, lymphadenopathy, ascites and lytic bone lesions. To evaluate for biochemical evidence of MC activation, a referral to an experienced allergist should be initiated. SM is a histopathologic diagnosis and requires a biopsy of the involved tissues, and bone marrow is the gold standard for this purpose. In general, clinicians should have a high index of suspicion for SM in those with **(1)** symptoms compatible with MC activation, **(2)** an elevated basal serum tryptase level, **(3)** biopsy-proven adult onset mastocytosis in the skin, and/or **(4)** unexplained bone findings. In addition, the histopathologic analysis should include a myeloid next-generation sequencing panel that includes genes such as *SRSF2*, *ASXL1*, *RUNX1*, mast cell immunophenotyping by immunohistochemistry and/or flow cytometry, and cytogenetics. In the presence of eosinophilia

and bone marrow MC proliferation, screening for the known tyrosine kinase gene fusions associated with myeloid or lymphoid neoplasms with eosinophilia (e.g. *FIP1L1-PDGFR*A) should be performed.^{29,30}

Diagnostic Criteria

The World Health Organization (WHO)^{29,31} and International Consensus Criteria (ICC)³⁰ are two classification systems used to establish the diagnosis of SM. The criteria are very similar but not entirely aligned. (nuances are summarized in the NCCN guideline²⁸ and Pardanani et al.²⁷) The main histopathologic feature used by both classification systems is the major criterion of multifocal dense aggregates (i.e. 15 or more MCs in aggregates) of MCs in the bone marrow or other extracutaneous tissue. Minor criteria include >25% of MCs with atypical morphology, any ligand-independent activating *KIT* mutation* (e.g. most commonly the *KIT* D816V mutation), an aberrant MC immunophenotype detected by flow cytometry or immunohistochemistry, and a baseline serum tryptase value of >20 ng/mL** (Table 1). The WHO requires 1 major and 1 minor criterion, or at least 3 minor criteria, and the ICC requires 1 major criterion or at least 3 minor criteria.^{29,30}

*The prevalence of *KIT* p.D816V mutations varies on the disease subtype (typical ISM >90%, SSM >90%, SM-AHN, >90%, ASM >80%, MCL <70%)

**In cases of SM-AHN, an elevated tryptase does not count as a SM minor criterion. The WHO states that basal serum tryptase level should be adjusted in case of hereditary alpha-tryptasaemia.

Staging

After the diagnosis of SM is established, it is important to then classify SM into specific subtypes (also known as variants) as this is important for understanding natural history and for planning treatment. This process can be confusing, which is further compounded by the subtle differences between the ICC and WHO criteria, which are summarized in Table 1. SM can be broadly divided into two major categories: non advanced SM and advanced SM. Non advanced SM includes three subtypes: bone marrow mastocytosis (BMM), indolent SM (ISM), and smouldering SM (SSM). The hallmark of non-advanced SM is that there is no significant end organ damage. Advanced

SM also includes three subtypes: aggressive SM (ASM), mast cell leukemia (MCL), and SM with associated hematological neoplasm (SM-AHN^a). The criteria used to classify all three indolent subtypes and the ASM subtype are the “B” and “C” findings (Table 2). The diagnosis of MCL requires the presence of at least 20% mast cells in bone marrow aspirate smears. The diagnosis of SM-AHN requires diagnostic criteria for both (1) SM and (2) another hematologic (myeloid or rarely lymphoid) neoplasm to be simultaneously fulfilled. Common AHNs that co-exist with SM are chronic myelomonocytic leukemia, myelodysplastic syndrome, myeloproliferative neoplasms, chronic eosinophilic leukemia, and acute myeloid leukemia.

Treatment

Mediator Symptoms, Anaphylaxis and Bone Health

Multidisciplinary collaboration, especially with allergists, is necessary to optimize patient care. MC activation symptoms greatly affect patients’ quality of life and are managed with anti-mediator therapies such as antihistamines, mast cell stabilizers, and leukotriene receptor antagonists. Counselling on trigger avoidance is crucial, especially with strategies to avoid insect bites and peri-procedural optimization.²⁸ It is recommended that all patients obtain a medical alert bracelet and/or wallet card, and must always carry two auto injectors of epinephrine with them at all times. All patients who have experienced anaphylaxis due to hymenoptera venom must be assessed by an allergist for venom immunotherapy and/or for omalizumab therapy for other severe allergic issues.^{28,32,33} Because of the risk of excessive bone loss, serial bone mineral density scans are an important part of management and bisphosphonates with antihistamines are typically used as front-line therapies.²⁸

Cytoreduction

Cytoreduction is typically indicated for those with end organ damage or with severe and refractory symptoms.^{26–28} Cytoreductive options include midostaurin, avapritinib, cladribine, peginterferon alfa-2a, and imatinib. Most international guidelines recommend enrolment in a clinical trial, midostaurin or avapritinib as front-line therapies for advanced SM, as well as cladribine when rapid debulking is required.^{26–28}

All variants must first meet SM diagnostic criteria	
Bone marrow mastocytosis ^a	
• SM established from bone marrow and no B findings, C findings, AHN or MCL	
• No skin involvement	
• Basal serum tryptase below 125 ng/mL	
Indolent SM	
• 0-1 B finding(s)	
• No C findings, AHN or MCL	
Smoldering SM	
• ≥ 2 B findings	
• No C findings, AHN or MCL	
Aggressive SM	
• ≥ 1 C finding	
• No AHN or MCL	
Systemic mastocytosis with Associated Hematological Neoplasm ^b	
• Meets SM diagnostic criteria and diagnostic criteria for second hematological neoplasm (usually a myeloid neoplasm)	
Mast Cell Leukemia	
• Bone marrow aspirate smears ≥ 20% MC^c	

Table 1. Criteria for systemic mastocytosis variants; *courtesy of Stephanie Lee, MD.*

a) In the 2022 WHO classification, BMM is a separate category from ISM. In the 2022 ICC classification, BMM is a subvariant of ISM.²⁹

b) In the 2022 ICC classification, this variant is named SM with an associated myeloid neoplasm (AMN) because overwhelmingly the concurrent neoplasms is myeloid origin.

c) The 2022 ICC states that MCs must be atypical immature cells, which include promastocytes, metachromatic blast-like cells, or highly pleomorphic mast cells. The ICC states in the presence of an inadequate bone marrow aspirate smear, MCL may be diagnosed by a diffuse, dense infiltration of atypical immature mast cells on bone marrow biopsy.³⁰

B findings reflect the disease burden but without organ dysfunction and C findings reflect disease burden with organ dysfunction.

B findings

2022 WHO

- >30% mast cells on bone marrow biopsy and serum total tryptase >200 ng/mL
- Signs of dysplasia or myeloproliferation in non-mast cell lineage, but criteria not met for a WHO AHN, with normal or only slightly abnormal blood counts
- Hepatomegaly without impaired liver function, palpable splenomegaly without hypersplenism and/or lymphadenopathy (palpation or imaging)
- KIT D816V variant allele frequency $\geq 10\%$

2022 ICC

- >30% of bone marrow cellularity by mast cells and serum total tryptase >200 ng/mL
- Cytopenia but not meeting criteria for C-findings or -cytosis. Reactive causes are excluded and criteria for myeloid neoplasms are not met.
- Hepatomegaly without impaired liver function, palpable splenomegaly without hypersplenism and/or lymphadenopathy >1 cm (palpation or imaging)

C findings

- Bone marrow dysfunction due to neoplastic mast cell infiltration defined as ≥ 1 cytopenia: absolute neutrophil count $< 1.0 \times 10^9/L$, hemoglobin < 100 g/L, and/or platelet count $< 100 \times 10^9/L$
- Palpable splenomegaly with hypersplenism
- Osteolytic lesion ≥ 2 cm
- Palpable hepatomegaly with impairment of liver function, and/or ascites, and/or portal hypertension
- Malabsorption with hypoalbuminemia +/- weight loss

Table 2. B- and C- Findings Criteria; *courtesy of Stephanie Lee, MD.*

Midostaurin is an oral multikinase inhibitor that has been approved for the treatment of advanced SM in Canada, the United States, and Europe. Two pivotal clinical trials have demonstrated the effectiveness of midostaurin in treating SM. The overall response rate (ORR) was approximately 60–69%, with median progression-free survival (PFS) and overall survival (OS) of 14 months and 29 months, respectively. All subvariants of advanced SM responded to the treatment, the patients reported an improved quality of life, and the main adverse events were GI toxicity and myelosuppression.^{34,35} Unfortunately, midostaurin is not funded in most provinces in Canada, and compassionate programs are extremely limited. Given that the annual out of pocket cost often exceeds \$100 000 CAD, midostaurin is not a realistic treatment option for most patients in Canada.

Avapritinib is a potent and selective inhibitor of the *KIT* D816V mutation that has been studied in the phase I EXPLORER and phase II PATHFINDER trials in adult patients with advanced SM.^{34,37} The interim analysis of the PATHFINDER trial showed an ORR of 75% at a median follow-up of 10.4 months and the estimated 12-month PFS and OS rates were 79% and 86%, respectively, at a median follow-up of 7 months. Intracranial bleeding was observed in 13% of patients in the EXPLORER trial and was strongly associated with severe thrombocytopenia³⁴; as a result, both studies were amended to exclude patients with severe thrombocytopenia, and avapritinib is recommended for patients with a platelet count of 50,000/mm³ or higher. Avapritinib was approved in the US in 2021 and in Europe in 2022 for the treatment of advanced SM but is not currently available in Canada.

Cladribine, while not approved by Health Canada for SM, is used off label for all variants of advanced SM. Studies have shown that cladribine has an ORR of approximately 50–77% for patients with advanced SM with a median duration of response of approximately 1–2.5 years. Infectious complications and myelosuppression are the main adverse events.^{38–40}

Peginterferon alfa-2a is also used off label in Canada for patients with ASM and SM-AHN (when the SM component requires treatment); however, it is not recommended for MCL.²⁸ It may also be useful in some patients with ISM or SSM who have severe or refractory mediator or bone symptoms.²⁸

Imatinib is approved by Health Canada for advanced SM for those without the *KIT* D816V

mutation or whose *KIT* mutational status is unknown; however, since >90% of patients with SM have the *KIT* D816V mutation, imatinib has a limited role in the treatment of SM.⁴¹

There is a paucity of high-quality data on the role of allogeneic hematopoietic stem cell transplant for patients with SM. Typically, this treatment is reserved for patients with aggressive/refractory disease and for those with SM-AHN with high-risk AHN features (e.g. AML). The role of KIT inhibitors in the post-transplant setting has not been formally studied in prospective trials.^{37,42}

Prognosis

Accurate staging of SM as described above is important for prognostication, but it is worth noting that most of the long-term survival data is from the pre-TKI treatment era.²⁷ Non advanced forms of SM are comparatively slow growing neoplasms and patients tend to have excellent long-term survival, ranging from a median OS not reached for BMM, 25–28 years for ISM, and 12 years for SMM.^{38,43,44} In ISM, the estimated rate of transformation to advanced SM and leukemic transformation is <3% and <1%, respectively.^{38,43,44} In advanced forms of SM, the median OS varies, with a range from approximately 3–6 years for those with ASM, 2–3 years for those with SM-AHN, and 2 months–2 years for those with MCL.^{28,38,45,46} Leukemic transformation in ASM and SM-AHN is variable, and is impacted greatly by the AHN component, with an overall risk ranging from 6–30%.³⁸ Prognostic models have been developed that integrate clinical and molecular variables, although the performance of these models in the TKI era is not well defined.^{27,28}

Conclusion

SM is a rare malignancy with a wide spectrum of clinical presentations and natural histories. The pathogenesis of SM is strongly linked to somatic *KIT*-activating mutations leading to **(1)** excessive MC activation, and **(2)** MC accumulation in tissues, which can lead to organ dysfunction and a high symptom burden that greatly impacts morbidity and/or mortality. Management requires multidisciplinary care, and while treatment options are expanding, they remain very limited in Canada, which is an enormous unmet need.

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Maintenance Therapy for CD20+ Indolent Lymphoma: **Who Should Receive Maintenance?**

Edward Koo, MD

David A. Macdonald, MD, FRCPC

Introduction

Maintenance rituximab (MR) has been a mainstay of treatment in Canada for CD20-positive indolent lymphoma for two decades. The adoption of MR into clinical practice occurred after the publication of the EORTC 20981 trial.¹ This trial showed a significant improvement in progression free survival (PFS) with two years of MR versus observation after induction therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with relapsed follicular lymphoma (FL). The use of MR was broadly extended to include its use in the front-line setting, following any R-containing inductions and including all CD20-positive indolent lymphoma histologies.

Automatic recommendations for MR became the standard practice for most patients. Given the recent changes to standard induction regimens in some indications, and with heightened concerns about infectious complications during B-cell depleting therapy, the recommendation for the use of MR should no longer be considered automatic. This review offers a balanced perspective of the evidence for MR.

Follicular Lymphoma

FL is the most common form of indolent non-Hodgkin lymphoma (NHL), with an estimated incidence of 38.3 cases per million individuals per year.² FL is incurable in most circumstances; therefore, consideration of maintenance therapy is important, given the goal to prolong the duration of response after induction therapy.

The PRIMA trial investigated MR in the front-line setting. In the trial, patients with untreated FL who received R-CHOP, rituximab

with cyclophosphamide, vincristine, and prednisone (R-CVP), or rituximab with fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) were randomized to 2 years of MR or observation without MR.³ At 9-years of follow-up, the median PFS was 10.5 years with MR compared with 4.1 years for those who underwent observation (hazard ratio (HR) 0.61; 95% confidence interval (CI), 0.52–0.73; $p < 0.001$), and the median time to the next line of treatment was not reached in the MR arm vs 6.1 years in the observation arm (HR 0.66; 95% CI, 0.55–0.78; $p < 0.001$). No improvement was demonstrated in overall survival.

In Canada, most centres use bendamustine plus rituximab (BR) as the preferred induction regimen based on the BRIGHT⁴ and StiL-NHL1 trials.⁵ Randomized controlled trial (RCT) data comparing MR to observation does not exist for patients receiving BR. However, a post hoc analysis conducted by the BRIGHT investigators using 5-year follow-up data found that patients who received MR after responding to BR had a significantly better PFS compared with those who did not receive MR (HR 0.50, 95% CI 0.26–0.94, $P = 0.030$), although no statistically significant difference was observed in overall survival (OS).⁶ The decision to assign a patient to MR was left to the investigators' discretion, which could have introduced bias into this data.

In a retrospective multi-institution analysis of 640 FL patients who received BR for FL, outcomes were compared between patients who received MR vs those who underwent observation.⁷ The 3-year PFS was higher for the MR group vs the observation group, (84.2% vs 61.2%), respectively ($p < 0.001$), as was the OS, (94.3% vs 85.1%) respectively, ($p = 0.001$). The decision to select patients for MR was left to the discretion of their treating physician, which prompted the investigators to conduct separate subgroup analyses of the MR effect based

on the patients' induction response. Amongst patients who achieved a complete response (CR), no difference was observed in the 3-year duration of response (DOR) or OS between those who underwent MR vs those who underwent observation. Among patients who achieved a partial response (PR), those who received MR had a longer 3-year DOR vs those who underwent observation, at 80% vs 45%, respectively ($p=0.003$), although no statistically significant difference in OS was observed. These findings indicated an improved DOR only in patients who achieved a PR but not a CR, compared to a PFS benefit across patients achieving both PR and CR in the randomized PRIMA study, suggests that patients who receive BR as induction therapy may not derive the same benefit from MR when compared to those receiving R-CHOP/R-CVP induction.

Regarding duration of maintenance, two years of MR has been commonly adopted, because it was used in the pivotal EORTC trial (an MR dose every 12 weeks) and in the PRIMA trial (a MR dose every 8 weeks). The retrospective analysis conducted by Hill et al. revealed heterogeneity in the administration of MR. The authors observed that MR was administered for a median of 18 months. They also observed a variety of dosing schedules, including every 2 months, every 3 months, and 4 weekly doses every 6 months. The StiL NHL7 MAINTAIN trial is currently investigating the difference between 2 and 4 years of MR. When the data was last presented in 2017, 4 years of MR demonstrated superior PFS compared with 2 years of MR, with no difference observed in OS, although it must be emphasized that the analysis is ongoing.⁸

The risks of toxicity must be considered given that most patients with FL typically have a favourable long-term prognosis.⁹ In the PRIMA study, MR was associated with a higher rate of Grade 3–4 adverse events, primarily cytopenias (5.2% in the MR group vs 1.6% in the observation group) and infections (4.4% in the MR group vs 1.0% in the observation group).³ Bendamustine has lymphodepleting effects, and when it is used in combination with anti-CD20 treatment, the risks of cytopenias, infection, and poor response to vaccination are increased. The GALLIUM study randomized FL patients to rituximab-based immunochemotherapy plus MR versus obinutuzumab-based immunochemotherapy plus maintenance obinutuzumab, in which the chemotherapy regimen was according

to a centre-specific choice of CHOP, CVP or bendamustine.¹⁰ During the maintenance phase approximately 12.8–16.7% of patients who had received bendamustine for induction experienced Grade 3–5 infections, which were almost double those of patients who received induction CVP (2.3–8.8%) or CHOP (3.9–5.9%). In a retrospective analysis comparing patients treated with BR to those treated with R-CHOP/R-CVP for FL in Ontario, admissions for infection were significantly more frequent in patients who received maintenance therapy after BR.¹¹

Regarding induction with single-agent rituximab (administered as four weekly doses), the phase III RESORT RCT compared MR to rituximab re-treatment (administered as a single dose every 13 weeks until treatment failure) and showed no difference in time to treatment failure.¹² In recent studies, long-term secondary outcomes have shown superiority for MR for freedom from cytotoxic therapy and response duration; however, no OS benefit was observed. Of note, these results are less relevant to Canadian practice, in which rituximab monotherapy induction is infrequently used.

Mantle Cell Lymphoma

Standard therapy for patients with mantle cell lymphoma (MCL) includes rituximab and a chemotherapy regimen selected based on transplant eligibility. The MCL Elderly Phase III RCT randomized patients over the age of 65 to receive rituximab with fludarabine and cyclophosphamide (R-FC) or R-CHOP induction, with a second randomization to maintenance therapy with rituximab or interferon-alpha until progression. Aside from demonstrating OS improvements with R-CHOP, those who received MR after R-CHOP but not after R-FC demonstrated benefits in both PFS and OS.¹³ Transplant ineligible patients are most commonly treated with BR. Subgroup analysis of the MCL cohort in the BRIGHT study showed a similar benefit in PFS but not in OS, though there appears to be more supportive evidence when compared to FL.⁴ In a US real-world retrospective analysis, the combination of BR followed by MR was associated with a significantly improved real-world time to next treatment (TTNT) vs BR alone, (65.4 months, 95% CI 61.6–75.6 vs 37.7 months, 95% CI 33.1–41.2) respectively ($p<0.001$) and OS, (89.5 months, 95% CI 80.0–108.6 vs 78.1 months, 95% CI 62.9–93.5), respectively ($p<0.001$).¹⁴

The standard of care for transplant eligible MCL patients is rituximab and cytarabine-containing chemotherapy, followed by autologous stem cell transplantation (ASCT). The use of MR post-ASCT is strongly supported. In the phase III LyMa trial, patients aged less than 66 years were randomized to MR for 2 years versus observation following rituximab, dexamethasone, cytarabine, cisplatin (R-DHAP) induction and ASCT. At 7 years of follow-up, MR was associated with an improvement in event-free survival and PFS.¹⁵ A systematic review and meta-analysis that examined 6 RCTs with similar inclusion criteria including MR in MCL outcomes, found PFS improvements with MR, specifically after R-CHOP or cytarabine containing induction, and after R-CHOP in the relapse setting.¹⁶

Waldenstrom's Macroglobulinemia

Treatment options in Waldenstrom's Macroglobulinemia (WM) differ somewhat from those for FL. WM treatment may involve more frequent use of single agent rituximab, as well as the particular activity of agents such as proteasome inhibitors and Bruton's tyrosine kinase inhibitors, among others.¹⁷ BR remains a commonly used induction regimen. The Phase III NHL-2008 MAINTAIN RCT compared rituximab maintenance every 2 months for 2 years to observation in patients treated with 6 cycles of BR, and found no statistically significant difference in PFS or in OS (the latter was not reached with both arms).¹⁸ MR as standard therapy for WM or lymphoblastic lymphoma is not currently recommended according to both the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines.

Marginal Zone Lymphoma

The common use of MR after induction BR in marginal zone lymphoma (MZL) in Canada is based on an extrapolation of the MR data from FL. However, no RCT has been conducted in this patient population. A subgroup of non-follicular lymphoma patients treated in the RESORT trial included 71 patients with MZL and 57 patients with small lymphocytic lymphoma (SLL).¹⁹ Results for those with MZL and SLL were similar to those for the FL group, with MR in responders resulting in an improvement in the median time to treatment failure and the median time to first cytotoxic therapy. This

study is cited by the NCCN as support for including MR as an optional first-line extended therapy in MZL. However, similar to FL, the use of single agent rituximab for induction is rarely chosen for patients with MZL in Canada, which reduces the relevance of this data.

Anti-CD20 Therapy and COVID-19

The COVID-19 pandemic has influenced the risk-benefit discussion of MR. A number of studies have demonstrated impaired responses to vaccination in patients with hematologic malignancies who have received anti-CD20 therapy,^{20,21} and worse outcomes for these patients when they contract COVID-19.^{22,23} A multi-centre retrospective study that included 16 French hospitals evaluated 111 lymphoma patients who were admitted to hospital in March and April 2020 with COVID-19.²⁰ The study reported that 85% of the patients had B-cell NHL and 71% had received treatment for lymphoma within 12 months prior to admission (63% had received anti-CD20 therapy). Recent anti-CD20 therapy was associated with prolonged length of stay (HR 2.26, 95% confidence interval 1.42–3.6, $p < 0.001$) and higher risk of death (HR 2.17, C.I. 1.04–4.52, $p = 0.039$).

The French cohort was an unvaccinated population who were admitted to the hospital at the onset of the pandemic. A recent meta-analysis examining COVID-19 outcomes in lymphoma and non-lymphoma indications,²¹ including studies published up to June 2023, which also accounts for vaccinated patients, showed that anti-CD20 use was associated with a significantly increased risk of severe illness (pooled OR 2.95, CI 2.30–3.78) and mortality (pooled OR 2.14, CI 1.37–3.35).

Summary

Ultimately, deciding upon MR in our current era of first-line treatment for CD20-positive indolent lymphoma requires an individualized assessment of the associated risks and benefits. In MCL, the evidence that supports the benefit of MR is clear, both after ASCT, and after BR induction in non ASCT-eligible patients. In WM, RCT data has shown a lack of benefit. In MZL there is simply a paucity of data. In FL, the magnitude of benefit with MR after RCHOP/RCVP is profound, with more than a doubling of the median PFS from 4 years to 10 years. However, while MR after BR already improves PFS to nearly 6 years

Trial/Design	Patient no.	Induction Treatment	Comparison	Outcome
Rummel et al. (StiL-NHL1)/RCT ⁴	447	BR vs R-CHOP	No maintenance in either arm	mPFS: 69.5 months vs 31.2 months OS: not statistically significant (p=0.249) mTTNT: NR (95% CI 124.9 –NR) vs 56 months (95% CI 39.1–82.0)
Follicular Lymphoma				
Bachy et al. (PRIMA)/RCT ²	1018	R-CHOP or R-CVP or R-FCM	MR x 2 years vs observation	PFS: 10.5 years vs 4.1 years (p<0.001) OS: NR vs NR (p=0.7948) TTNCT: NR vs 9.3 y (p<0.001)
Kahl et al. (RESORT)/RCT ¹¹	289	Rituximab x 4 doses	MR vs rituximab re-treatment	7-year freedom from first cytotoxic therapy: 83% vs 63% (p=0.001) OS: 83% vs 84% (p=0.5972)
Hill et al./retrospective analysis ⁶	640	BR	MR vs observation	3-year PFS: 84.2% vs 61.2% (p<0.001) 3-year OS: 94.3% vs 85.1% (p=0.001)
Mantle Cell Lymphoma				
Sarkozy et al. (LyMA)/RCT ¹⁴	240	R-DHAP + autologous stem cell transplantation	MR x 2 years vs observation	EFS: NR vs 5.8 years (p<0.0001) PFS: NR vs 6.1 years 7-year OS estimate: 83.2% vs 72.2% (p=0.087)
Waldenstrom's Macroglobulinemia				
Rummel et al. (StiL-NHL7-2008 MAINTAIN)/RCT ¹⁷	288	BR	MR vs observation	PFS: 101 months vs 83 months (p=0.32) OS: NR for both arms

Table 1. Summary of relevant randomized controlled trials addressing maintenance therapy for CD20+ indolent lymphoma; courtesy of Edward Koo, MD and David A. MacDonald, MD, FRCPC.

Abbreviations: BR: bendamustine, rituximab; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **R-CVP:** rituximab, cyclophosphamide, vincristine, prednisone; **R-FCM:** rituximab, fludarabine, cyclophosphamide, mitoxantrone; **R-DHAP:** rituximab, dexamethasone, cytarabine, cisplatin; **MR:** maintenance rituximab; **PFS:** progression-free survival; **OS:** overall survival; **TTNT:** time to next treatment; **TTNCT:** time to next chemotherapy treatment; **EFS:** event-free survival; **NR:** not reached

without maintenance, there is no Level 1 evidence supporting the additional benefit of MR.

A discussion about MR or observation with an FL patient after induction BR should include the following important points. An acknowledgement that the best evidence supporting MR is extrapolated from a population of patients that received inferior induction treatment. That the

depth of response after induction (CR or PR) may influence the degree of benefit from MR. That there is clear evidence of potential infectious and COVID-related risks. Finally, that the goal of prolongation of the present remission status should be tempered with the knowledge that more effective subsequent treatments are emerging (**Table 1**).

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