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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] respectively. 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

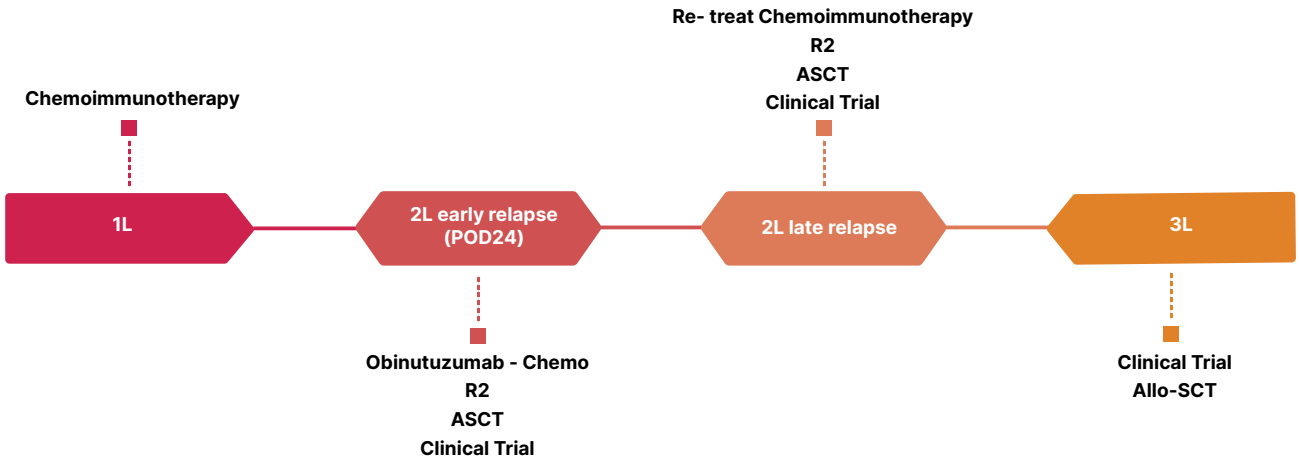
Two chimeric antigen receptor (CAR) T-cell therapies are Health Canada approved with final funding decisions having been rendered for RR FL after ≥ 2 prior lines of therapy: axicabtagene ciloleucel (axi-cel), a CD28-based agent and tisagenlecleucel (tisa-cel) a 4-1BB based CAR T product.[47,48] CADTH 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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