Review

A Canadian Evidence-Based Guideline for the First-Line Treatment of Follicular Lymphoma: Joint Consensus of the Lymphoma Canada Scientific Advisory Board

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Abstract

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL) in North America. Because of the heterogeneity of the disease, treatment options vary from observation to aggressive therapies or stem cell transplantation, or both. Although advances in treatment have improved outcomes, the disease remains largely incurable. In Canada, no unified national guideline exists for the front-line treatment of FL; provincial guidelines vary and are largely based on funding. There is therefore a need for evidence-based national treatment guidelines that are supported by Canadian hematologists to ensure that patients with FL have equitable access to the best available care. A group of experts from across Canada developed a national evidence-based treatment guideline to provide health care professionals with clear guidance on the first-line management of FL. Results of a systematic review of the literature are presented with consensus recommendations based on available evidence.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 2, 59-74 © 2015 Elsevier Inc. All rights reserved.
Keywords: Canadian, Follicular lymphoma, Guidelines, Hematology, Indolent lymphoma, Lymphoma

Introduction

Follicular lymphoma (FL) is the most common indolent (or low-grade) form of non-Hodgkin lymphoma (NHL) and the second most common form of all NHLs, composing up to 35% of all cases in North America and 9% to 22% worldwide.[1-5] In Canada, NHL was estimated to account for 4.2% of all new cancer cases in 2013.[6] Furthermore, between 1998 and 2007, there was a significant increase in the incidence rate of NHL in male patients (by 0.8% per year) and a numeric (but not significant) increase in female patients (by 0.4% per year).[6] In Canada, the incidence and prevalence of FL specifically are > 1500 cases and > 20,000 cases, respectively, per year.[7]

FL is staged using the Ann Arbor classification, in which stages I and II are considered limited or localized disease, and stages III and IV are considered advanced disease.[8] For all stages, patients presenting with traditional B symptoms (fever, night sweats, and weight loss) are considered symptomatic.[8] Other symptoms might include painful adenopathy/splenomegaly or locally obstructing symptoms. However, many patients, even some with advanced-stage disease, are asymptomatic. In addition to B symptoms, the Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria are commonly used to identify patients requiring immediate treatment.[4,9]

FL is further classified into histologic grades based on the World Health Organization (WHO) classification.[10] WHO categorizes FL into low grade (formerly grades 1 and 2) and high grade (previously grade 3a).[4,10] Diffuse areas in any grade 3 FL (previously grade 3b) should be designated as diffuse large B-cell lymphoma (DLBCL) and is typically treated as such. After diagnosis, the Follicular Lymphoma International Prognostic Index (FLIPI) and revised FLIPI2 may be determined for prognostic purposes.[11,12]

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Submitted: May 6, 2014; Revised: Jul 18, 2014; Accepted: Jul 29, 2014; Epub: Aug 2, 2014

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2152-2650/$ - see frontmatter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clml.2014.07.015

Because of the heterogeneity of this disease, treatment options for patients with FL tend to be controversial and vary from observation (or "watch and wait") to stem cell transplantation (SCT).[13,14] With advances in treatment, patients with FL have shown improved outcomes; however, a curative treatment is still not available, particularly for advanced-stage disease.[4,13,15] Accordingly, the overarching goal of treatment is to achieve effective and durable disease control (ie, prolong overall survival [OS] and progression-free survival [PFS]) with minimal toxicity, while maintaining quality of life (QoL).[4,13,14]

Several international guidelines exist for FL, including the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), the British Committee for Standards in Haematology, the Italian Society of Hematology/Italian Society of Experimental Hematology/Italian Group for Bone Marrow Transplantation, as well as Spanish guidelines.[16-20] However, in Canada, there is no unified national guideline for FL. Although provincial guidelines exist, they differ across provinces and are primarily based on the availability of agents in the provincial formulary.[21,22] Accordingly, there is a need for evidence-based national treatment guidelines that are supported by Canadian hematologists to ensure that patients with FL in Canada have equitable access to the best available care.[23] Therefore, a group of experts from across Canada, including representation from Ontario, Quebec, Nova Scotia, British Columbia, and Alberta, developed a national evidence-based treatment guideline in association with Lymphoma Canada to provide health care professionals with clear guidance on the first-line management of patients with FL.

Target Population

The current guideline is for the primary treatment of adult patients with FL. Any patients with DLBCL or grade 3b FL should be treated according to DLBCL guidelines, and a discussion of their treatment is beyond the scope of this guideline.

Guideline Questions

1. What treatment options should be considered for localized FL?
2. How should asymptomatic advanced-stage FL be managed?
3. What treatment options should be considered for symptomatic advanced-stage FL?
4. In which patients should additional treatment be considered (ie, maintenance, consolidation, SCT)?

Methodology

When available, publications based on only phase III studies were included in the literature review. When few randomized trials were identified, we considered prospective studies. When few prospective studies were identified, we considered retrospective and institutional-level studies with a study sample of at least 20 patients. Publications in languages other than English were excluded. Relevant existing international practice guidelines from NCCN, ESMO, the British Committee for Standards in Haematology, the American College of Radiology, the Italian Society of Hematology/Italian Society of Experimental Hematology/Italian Group for Bone Marrow Transplantation, and Spain, as well as those from the Alberta Health Services, British Columbia Cancer Agency (BCCA), Cancer Care Nova Scotia, and Cancer Care Ontario, were also reviewed. Further details on methodology are included within each section of the guidelines that follow.

The expert panel used the NCCN categories of evidence and consensus to grade the level of evidence supporting recommendations.[24] Details of the NCCN categories are presented in Table 1.

Question 1: What treatment options should be considered for localized FL?

Background

Although the vast majority of patients are diagnosed with advanced FL, approximately 15% to 30% present with localized (stage I or II) disease.[25-27] Treatment of localized FL remains poorly defined and controversial because of a lack of randomized phase III trials in this uncommon subpopulation. Accordingly, based on data from retrospective series, radiotherapy (RT) is considered the standard of care for localized FL by North American and European guidelines, as well as provincial guidelines in Canada.[16-22] Alternative treatment options being examined in clinical trials include observation (ie, watch and wait [WW]) and combined modality therapies, such as chemotherapy or immunotherapy, or both, with and without RT. Furthermore, to the best of our knowledge, no current guidelines or literature distinguishes between asymptomatic and symptomatic localized FL; therefore, it is unclear if both presentations should be treated similarly.

Methodology

A literature search was performed using the following terms: follicular, indolent, lymphoma, stage I, stage 2, localized, limited, first-line, front-line, primary, asymptomatic, and symptomatic. When few randomized trials were identified, we considered prospective studies. When few prospective studies were identified, we considered retrospective and institutional-level studies with a study sample of at least 20 patients. Studies including patients with histologic types other than FL were eliminated from the literature review, with the exception of 1 study determined to be of key importance in determining the optimal dose of RT. All searches were limited to the years 2000 through 2014.

Radiotherapy

A total of 2 prospective and 10 retrospective studies examining RT in localized FL were found (Table 2).[25-35] In identified studies, the median age of patients with localized FL generally ranged from 50 to 64 years. Although a few studies reported that age was an independent prognostic factor for outcome, with younger age being

Table 1 NCCN Categories of Evidence and Consensus

Category 1	Based on high-level evidence, there is uniform consensus that the intervention is appropriate
Category 2A	Based on lower-level evidence, there is uniform consensus that the intervention is appropriate
Category 2B	Based on lower-level evidence, there is consensus that the intervention is appropriate
Category 3	Based on any level of evidence, there is major disagreement that the intervention is appropriate

Table 2 Studies of Radiation Therapy in Localized Follicular Lymphoma

Reference	Treatment (Dose/ Field)	N	NHL Type/ Stage I/II/III (%)	Median Follow-Up (years)	OS	Remission Duration	CSS/DSS	Response Rates
Prospective Studies								
Lowry et al, 2011[36,a] Multicenter BNLI and NCRI	40–45 Gy versus 24 Gy for indolent NHL IFRT	Total: 1001 (WHO diagnosis: 765)	Any NHL FL grade 1/2: 171	5.6	5-years OS: 74% for 24 Gy, 73% for 40-45 Gy ($P = .84$)	5-years FFLP: 75.6% for 24 Gy, 78.9% for 40-45 Gy ($P = .59$)	NG	ORR: 92% for 24 Gy, 93% for 40-45 Gy ($P = .72$) CR: 82% for 24 Gy, 79% for 40-45 Gy PR: 10% for 24 Gy, 14% for 40-45 Gy SD/PD: 8% for 24 Gy, 7% for 40-45 Gy
Ha et al, 2003[30] Single center; University of Texas MD Anderson Cancer Center	30–30.6 Gy CLI	47	FL 10.6/29.8/59.6	4.5 (in 45 of 47 surviving patients)	5 years: 94% (Stages I/II/III: 100%/ 100%/91%; $P = .56$)	5-years FFP: 53% (Stages I/II/III: 33%/72%/50%; $P = .77$)	NG	CR: 98% PD: 2%
Retrospective Studies								
Frank et al, 2001[29] Single center	25.5–50 Gy IFRT/EFRT/ TLI/TNI: n = 19/13/11/3 n = 1 for local therapy	47	FL 46.8/29.8/23.4	6.58	Stages I/II 5 years: 85% for EFRT/TLI, 83% for IFRT (NS) Stage III 5 years: 73%	Stages I/II 5-years RFS: 73% for EFRT/TLI, 61% for IFRT (NS) Stage III 5-years FFP: 27%	NG	CR: 96%
Wilder et al, 2001[28] Single center; University of Texas MD Anderson Cancer Center	26.2–50.0 Gy IFRT/IRRT/EFRT: 9%/54%/37%	80 RT alone	FL 41/59/0	19 (of 20 surviving patients)	15 years: 43% (Stage I vs. stage II: 44% vs. 43%; $P = .67$ IFRT/IRRT versus EFRT: 40% versus 49%; ($P = .51$)	15-years PFS: 41% (Stage I vs. stage II: 66% vs. 26%; $P = .006$)	15-years CSS: 87% versus 54% (Stage I vs. stage II; $P = .01$; IFRT/IRRT vs. EFRT: 72% vs. 59%; $P = .36$)	NG
Guadagnolo et al, 2006[31] Multicenter; Boston	30–42 Gy IFRT/IRRT/EFRT/TBI	Total: 106 RT alone: n = 79; IFRT/ IRRT: n = 75	FL 74/26/0	12	10 years: RT alone: 74%; IFRT/IRRT: 72% 15 years: RT alone: 62%; IFRT/IRRT: 59%	FFTF: 10 years: RT alone: 47%; IFRT/IRRT: 46% 15 years: RT alone: 43%; IFRT/IRRT: 42%	NG	NG
Campbell et al, 2010[27] BCCA Lymphoid Cancer database	20–40 Gy IRRT/INRT≤ 5 cm	Total: 237 IRRT: 142; INRT ≤ 5 cm: 95	FL 76/24/0	7.3	5 years: 85% 10 years: 66% (IRRT vs. INRT ≤ 5 cm: 71% vs. 59%; $P = .013$) 15 years: 46% Median: 80 mo	PFS: 5 years: 66% 10 years: 49% (IRRT vs. INRT ≤ 5 cm: 48% vs. 50%; $P = .498$) 15 years: 43% Median: 51 mo	DSS: 5 years: 92% 10 years: 82% (IRRT vs. INRT ≤ 5 cm: 85% vs. 78%; $P = .142$) 15 years: 68% 20 years: 62%	NG
Pugh et al, 2010[25] SEER database	35–50 Gy[b]	Total: 6568 RT alone: 2222	FL 67/33/0 RT alone: 77/23/0	5.5	5 years: 81% 10 years: 62% 15 years: 45% 20 years: 35% (All data for RT alone)	NG	DSS: 5 years: 90% 10 years: 79% 15 years: 68% 20 years: 63% (All data for RT alone)	NG

Table 2 Continued

Reference	Treatment (Dose/ Field)	N	NHL Type/ Stage I/II/III (%)	Median Follow-Up (years)	OS	Remission Duration	CSS/DSS	Response Rates
Guckenberger et al, 2012[32] Single center	25–50 Gy and 12.6–45 Gy a median of 30 d later EFRT/TNI	Total: 107	FL 46.7/33.6/19.6	10 (all); 14 (living)	10 years: 64% 15 years: 50% (Stages I/II/III: 51%/45%/54%; NS; EFRT/TNI: 34%/65%)	FFP: 5 years: 76% 10 years: 58% (Stages I/II/III: 74%/40%/62%; stage I vs. stage II $P = .001$; EFRT/TNI: 54%/62%; NS) 15 years: 56%	NG	NG
Fakhrian et al, 2012[33] Single center	26–56 Gy IFRT/EFRT	Total: 50	FL 60/30/10	8	2 years: 96% (Stage I vs. stage II: 100% vs. 93%) 5 years: 90% (Stage I vs. stage II: 100% vs. 69%) 10 years: 70% (Stage I vs. stage II: 87% vs. 52%; IFRT vs. EFRT: 71% vs. 68%; $P = .19$) Median: 18 years	EFS: 2 years: 90% 5 years: 70% 10 years: 38% (Stage I vs. stage II: 36% vs. 37%; IFRT vs. EFRT: 23% vs. 43%; $P = .84$) Median: 7 years	NG	CR: 78% PR: 18%
Friedberg et al, 2012[35] National LymphoCare database	RT[b,c]	Total: 206 RT alone: 56	FL 100/0/0	4.75	NG	PFS: 4.75 years: 68% Median: 6 years	NG	NG
Ahmed et al, 2013[34] Single center; Manitoba Cancer Registry	15–48 Gy IFRT/EFRT	40	FL 65/35/0	6.9	5 years: 86% 10 years: 59% Median: 13 years	PFS: 5 years: 67% 10 years: 54% EFS: 5 years: 60% 10 years: 22% Median: 6.5 years	NG	CR: 100%
Michallet et al, 2013[26]	40–50 Gy IFRT/EFRT	Total: 145 RT alone: 21; IFRT: 16; EFRT: 5	FL Total: 57.9%/42.1%/ 0% RT alone: 90.5%/ 9.5%/0%	7.1	7.5 years: 66% (RT alone)	7.5 years PFS: 19% (RT alone)	NG	CR: 80.9% PR: 9.5% SD: 0% PD: 9.5% (All data for RT alone)

Abbreviations: BCCA = British Columbia Cancer Agency; BNLI = British National Lymphoma Investigation; CLI = central lymphatic irradiation; CR = complete response/remission; CSS = cause-specific survival; CT = chemotherapy; DFS = disease-free survival; DSS = disease-specific survival; EFRT = extended field radiotherapy; EFS = event-free survival; FFLP = freedom from local progression; FFP = freedom from progression; FFTF = freedom from treatment failure; FL = follicular lymphoma; IFRT = involved field radiotherapy; INRT (≤5 cm) = involved node radiotherapy (with margins up to 5 cm); IRRT = involved regional radiotherapy; NCRI = National Cancer Research Institute; NG = not given; NHL = non-Hodgkin lymphoma; NS = not significant; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response/remission; RFS = relapse-free survival; RR = response rate; RT = radiation therapy; SD = stable disease; SEER = Surveillance Epidemiology and End Results; STLI = subtotal lymphoid irradiation; TBI = total body irradiation; TLI = total lymphoid irradiation; TNI = total nodal irradiation.

[a]Despite including histologic types other than FL, this study was included based on its importance in determining the optimal dose of RT.

[b]Did not specify field size.

[c]Did not specify radiation dose.

more favorable, none assessed the long-term risks of RT in young patients.[25,27,31]

Data reported from existing studies show that RT confers excellent local tumor control (ie, overall response rate [ORR] and local control > 90%); however the 10- to 20-year PFS/relapse-free survival rate is approximately 50%, resulting in 10-year OS rates of approximately 50% to 75%. Although disease in nearly half of patients relapses within 10 years, relapse rates appear to plateau after 10 years, suggesting not only that the risk of relapse beyond 10 years is low but also that RT is potentially curative (Table 2).

Despite the positive outcomes reported, the majority of identified studies are complicated not only by their retrospective nature but also by the varied doses and fields of RT that were used. Radiation doses generally ranged from 15 to 56 Gy, and only 1 study compared low versus high radiation doses (Table 2). A phase III trial in the United Kingdom compared 24 Gy to 40 to 45 Gy in patients with indolent and aggressive lymphoma.[36] Results demonstrated no difference in ORR between the standard-dose and lower-dose arms (93% vs. 92%, respectively) and no significant difference in local control, remission duration, or OS. Among 248 patients who received radical RT as first-line therapy, there was no difference in PFS between the 24-Gy and 40- to 45-Gy arms. Consequently, except in unusual cases, doses of 24 to 30 Gy in 1.5- to 2-Gy fractions are typically recommended.[37]

A variety of different radiation field sizes has been reported in patients with localized FL. Radiation field sizes include, in order from largest to smallest volume, total body irradiation, total/central lymphoid irradiation, total nodal irradiation (TNI), extended-field RT (EFRT), involved regional RT (IRRT), involved field RT (IFRT), and involved nodal RT (INRT). Retrospective studies comparing various field sizes in patients with localized FL have found no significant differences in PFS or OS.[27-29,32,33] Given that the use of larger field sizes has not been found to improve OS and there are concerns about radiation-induced toxicity and secondary malignancy, IFRT has been considered the standard field size in clinical practice.[16-20]

Despite being considered the standard of care, RT for localized FL is greatly underused in the United States. A large Surveillance, Epidemiology, and End Results (SEER) database analysis of 6568 patients with low-grade localized FL in the United States found that RT was associated with significantly improved OS compared with non-RT approaches ($P < .0001$); however, only a third of the patients received upfront RT over the 30-year study period.[25] Few studies to date have comparatively evaluated the varied treatment approaches used for localized FL. In a retrospective analysis of the LymphoCare database, less than one third of patients (27%) with stage I FL were treated with RT.[35] The other first-line treatment strategies included rituximab plus chemotherapy (28%), observation (17%), rituximab monotherapy (12%), and combined modality with RT (13%), with the latter subgroup being more likely to have B symptoms and grade 3 histologic stage. After a median follow-up of 4.75 years, there were no differences in OS between the various approaches. However, after adjusting for tumor grade, lactate dehydrogenase, and the presence of B symptoms, PFS was significantly improved with either chemoimmunotherapy or combined modality treatment with RT versus RT alone. Another recent retrospective study divided patients into 6 groups according to their initial treatment: observation, RT alone, chemotherapy, RT with chemotherapy, rituximab monotherapy, and chemoimmunotherapy.[26] Similar to the findings of the LymphoCare database analysis, OS did not differ between treatments at 7.5 years, whereas PFS at 7.5 years was significantly higher with chemoimmunotherapy versus all other treatments ($P = .00135$).[26] Accordingly, although these studies challenge the use of RT alone as the standard of care for localized FL, they are limited by their retrospective design and small numbers of patients.

Combined Modality Therapies

Radiotherapy Plus Chemotherapy. Despite the fact that RT alone results in durable in-field tumor control rates of > 90%, relapse in new and out-of-field sites is the main cause of treatment failure.[38,39] Accordingly, the addition of chemotherapy to first-line RT may be an attractive alternative approach. A total of 4 studies evaluating the combination of chemotherapy with radiation in the rituximab era were identified (Table 3).[26,31,35,40] With the exception of 1 prospective study, most studies were retrospective, generally included few patients, and demonstrated conflicting results. In the relatively large nonrandomized prospective study of 85 patients with localized FL who were treated with chemotherapy (ie, 10 cycles of CHOP/CVP plus bleomycin [cyclophosphamide, vincristine, prednisone, and bleomycin with or without doxorubicin]) and IFRT (30-40 Gy), the 10-year time-to-treatment failure (TTF) and OS rates were 72% and 80%, respectively, and 99% of patients achieved complete remission.[40] Although these outcomes suggest a benefit of combining chemotherapy with RT compared with RT alone, there are no definitive data demonstrating a survival advantage. In light of the limited promising data, a randomized controlled phase III trial comparing IFRT and IFRT plus chemotherapy (ie, CVP) with rituximab in patients with localized FL was initiated in 2000 by the Trans-Tasman Radiation Oncology Group and the Australian Leukaemia and Lymphoma Group (NCT00115700). This trial is currently ongoing and is estimated to be completed in late 2022.

Chemotherapy or Immunotherapy, or Both. Despite the fact that FL is very radiosensitive, chemotherapy or immunotherapy without RT is used in about 40% of patients with localized disease, according to the US LymphoCare database data from 2004 to 2007.[35] In addition, a recent SEER database analysis demonstrated that only 34% of patients in the United States with early-stage FL were treated with RT.[35]

Only 2 retrospective studies assessing chemotherapy or immunotherapy, or both, in patients with localized FL were identified (Table 3).[26,35] No significant differences in OS were reported; however, regarding PFS, patients in both studies who received chemoimmunotherapy fared better than those who received RT alone. These findings should be interpreted with caution because these studies were retrospective and involved small numbers of patients.

Observation

Although observation is a common and reasonable approach used in patients with asymptomatic advanced FL (described later),

Table 3 Combined Modality Therapy in Localized Follicular Lymphoma

Reference	Treatment	N	NHL Type/ Stage I/II (%)	Median Follow-Up (years)	OS	Remission Duration	Response Rates
Prospective Studies							
Seymour et al, 2003[40] Single center; University of Texas MD Anderson Cancer Center	COP-Bleo/ CHOP-Bleo + RT (30–40 Gy)	Total: 102 (FL only: 85)	FL 45 of 55	10	5 years: 91% (FL only) 10 years: 80% (FL only; Stage I vs. stage II: 71% vs. 87%; $P = .02$)	TTF: 5 years: 80% (FL only) 10 years: 72% (FL only; Stage I vs. stage II: 73% vs. 70%; $P = 0.7$)	CR/CRu: 99% (n = 77 of 78)
Retrospective Studies							
Guadagnolo et al, 2006[31] Multicenter; Boston	CHOP/ CHOP + CVP/ CVP/CP/ CMOPP/ M-BACOD/ M-ACOD + RT (30–42 Gy)	Total: 106 (RT + CT: 27)	FL 74/26	12	10 years: 78% 15 years: 57% (Data are for RT + CT)	FFTF: 10 years: 46% 15 years: 31% (Data are for RT + CT)	NG
Friedberg et al, 2012[35] National LymphoCare database	RT + CT (R-CHOP/R-CVP); R; or R-CT (R-CHOP/ R-CVP)	Total: 206 (RT + CT: 26; R: 25; R-CT: 57)	FL 100/0	4.75	NG	4.75 years PFS: RT + CT: 96%; R: 76%; R-CT: 84%	NG
Michallet et al, 2013[26]	RT + CT (CHOP and CHOP-like regimens); R-CT; CT; R	Total: 145 (RT + CT: 19; R-CT: 36; CT: 26; R: 7)	FL 57.9/42.1	7.1	7.5 years: 67% (RT + CT); 74% (R-CT); 74% (CT); 100% (R)	7.5 years PFS: 26% (RT + CT); 60% (R-CT); 23% (CT); NA (R)	CR: 94.7%, PR: 5.3% (RT + CT); CR: 75%, PR: 16.7% (R-CT); CR: 69.2%, PR: 19.2% (CT); CR: 57.1%; PR: 42.9% (R)

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP-Bleo = cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin; CMOPP = cyclophosphamide, nitrogen mustard (mechlorethamine), vincristine, procarbazine, and prednisone; COP-Bleo = cyclophosphamide, vincristine, prednisone, and bleomycin; CR = complete response/remission; CRu = complete response/remission unconfirmed; CSS = cause-specific survival; CT = chemotherapy; CVP = cyclophosphamide, vincristine, and prednisone; DFS = disease-free survival; FFTF = freedom from treatment failure; FL = follicular lymphoma; M-ACOD = methotrexate, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; M-BACOD = methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; NA = not available; NHL = non-Hodgkin lymphoma; NS = not significant; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response/remission; R = rituximab; RR = response rate; RT = radiation therapy; SD = stable disease; TTF = time to treatment failure.

its use in localized disease is controversial because no prospective randomized controlled studies have been conducted in this population. Three retrospective studies investigating observation as the first-line approach in localized FL were identified (Table 4).[26,35,41] A retrospective analysis of 43 patients with low-grade asymptomatic localized FL in whom treatment was deferred for at least 3 months reported 5-, 10-, 15-, and 20-year OS rates of 97%, 85%, 58%, and 22%, respectively.[41] After a median follow-up of 7.2 years, more than half of the patients (63%) did not require treatment, suggesting that deferred therapy may be an acceptable approach in asymptomatic localized FL.[41] Reasons for no initial therapy included concerns about potential complications of RT, patient or physician preference, and advanced age or comorbidities. In 2 recent retrospective studies of patients with localized FL treated with variable treatment options, including observation, no differences in OS were reported, suggesting that observation may be a reasonable strategy in the first-line setting in selected cases.[26,35]

Recommendation 1 (Level of Evidence: Category 2A). Although RT is considered the standard of care, it is difficult to claim that RT is better than other therapies, because there is a lack of prospective randomized controlled trials justifying high-level evidence-based recommendations. However, in light of the indolent nature of FL, and thereby the inherent necessity of long-term follow-up, as well as the relative rarity of localized FL, it should be kept in mind that randomized phase III trials are difficult to conduct in this population. Accordingly, RT should be considered the preferred treatment for localized FL.

Recommendation 2 (Level of Evidence: Category 1). Outside of clinical trials, lower doses—24 to 30 Gy in 1.5- to 2-Gy fractions—and smaller field sizes for RT are most appropriate given the potential for long-term toxicity.

Recommendation 3 (Level of Evidence: Category 2B). Although emerging data using combined modality treatments are promising, existing data are limited and there are no randomized phase III trials. If outcomes from randomized studies prove positive, combined modality treatments may present additional options for patients with localized disease.

Recommendation 4 (Level of Evidence: Category 2B). When either the potential toxicity of RT outweighs the potential benefits or the patient refuses RT, observation alone may be a reasonable alternative.

Question 2: How should asymptomatic advanced-stage FL be managed?

Background

Canadian provincial guidelines for the treatment of asymptomatic, advanced-stage FL are available for Alberta and British Columbia (BC). The Alberta guidelines recommend the initiation of systemic treatment in patients with stage III/IV or bulky stage I/II disease who have symptoms (eg, fever, night sweats, weight loss, malaise, pain, or nausea); significant lymphadenopathy (eg, > 7-cm mass, > 3 sites, and > 3 cm, or rapidly progressive); splenomegaly > 6 cm below costal margin, hypersplenism, or pain; impending organ compromise (eg, compression, pleural/pericardial effusions, ascites); cytopenia secondary to bone marrow infiltration; or those with a preference because of anxiety and poor QoL without treatment.[21] International guidelines similarly recommend the initiation of systemic treatment on identification of symptoms such as B symptoms, hematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression.[16-20]

Both the Alberta and BC guidelines state that close follow-up under continued observation (WW) is appropriate for patients without requirement for systemic treatment.[21,22] In addition, the Alberta guidelines recommend that in the absence of symptoms, patients may choose systemic treatment based on anxiety or poor QoL. The BC guidelines also state that patients with asymptomatic advanced-stage FL without requirement for systemic therapy within 6 months of diagnosis are eligible to receive rituximab monotherapy.

Methodology

We performed a systematic literature search including the search terms watch, wait, and FL, and asymptomatic, watch, and wait. The search included only randomized studies, and only studies published in the era before rituximab were included. However, in the rituximab era, we included 1 abstract in our report because of the importance of this study in the discussion of this topic.

Table 4 Studies of Observation (Watch and Wait) in Localized Follicular Lymphoma

Reference	Treatment	N	NHL Type/ Stage I/II (%)	Median Follow-Up (years)	OS	Remission Duration
Advani et al, 2004[41] Retrospective; Stanford University Lymphoma database	No initial therapy	43	FL 26/74	7.2	5 years: 97% 10 years: 85% 15 years: 58% 20 years: 22%	NG
Friedberg et al, 2012[35] Retrospective; National LymphoCare database	Observation	Total: 206 (WW only: 35)	FL 100/0	4.75	NG	4.75-years PFS: 74%
Michallet et al, 2013[26] Retrospective	Observation	Total: 145 (WW only: 36)	FL 61.1/38.9	7.1	7.5 years: 72% (WW only)	7.5-years PFS: 26% (WW only)

Abbreviations: NG = not given; NHL = non-Hodgkin lymphoma; OS = overall survival; PFS = progression-free survival; WW = watch-and-wait.

Guideline for Follicular Lymphoma Treatment

Era Before Rituximab. A total of 3 published randomized trials were found that compared first-line treatment with chemotherapy versus WW alone at diagnosis in asymptomatic patients (Table 5).[42-44] The GELF and the BNLI used defined criteria for patients in whom immediate therapy was not felt to be indicated (Table 6). No trials showed a significant difference in OS between WW groups and those given early treatment (Table 5).

Rituximab Era. For the rituximab era, there were no studies found examining early treatment with rituximab plus chemotherapy. Results from 1 published study and 1 abstract examining early treatment with rituximab monotherapy are reported in Table 5.[45,46] One published randomized study by Ardeshna et al (2014) compared rituximab to WW in asymptomatic patients.[46] About 95% of patients had low tumor burden (GELF criteria); the other 5% had raised lactate dehydrogenase levels but fulfilled the remaining GELF criteria. Preliminary results showed that significantly fewer patients required further treatment, and longer PFS was reported in those initially treated with rituximab (Table 5). Additionally, an improvement in the Mental Adjustment to Cancer Scale score and Illness Coping Style score was demonstrated in patients given rituximab versus those in the WW arm.[46] An abstract by Kahl et al (2011) included patients with low tumor burden FL (GELF) given rituximab induction and randomized (for those responding to induction) to rituximab maintenance (R-maintenance) or rituximab retreatment at progression. Time to treatment failure (TTF) was 3.6 years in the rituximab retreatment and 3.9 years in the R-maintenance arm, with no statistical difference between groups.

Recommendation 1 (Level of Evidence: Category 2A). Criteria for initiation of chemoimmunotherapy should be based on the identification of symptoms as defined by the GELF or BNLI criteria.

Recommendation 2 (Level of Evidence: Category 1). In asymptomatic advanced FL, we do not recommend the use of chemoimmunotherapy or chemotherapy alone as early treatment because of the lack of published randomized studies. We therefore recommend observation alone in patients who do not fulfill the indications for treatment with chemoimmunotherapy.

Table 5 Randomized Studies Comparing Treatment to Observation in Asymptomatic Advanced-Stage Follicular Lymphoma

Reference	N	Treatment Groups	Median Follow-Up (years)	Efficacy Results
Era Before Rituximab				
Young et al, 1988[44] NCI	104	Arm 1 (n = 44): WW Arm 2 (n = 60; 15 not randomly assigned): ProMACE-MOPP + TNI	5	FFT: 56% in WW arm Median time to crossover: 34 mo
Brice et al, 1997[43] GELF	193	Arm 1 (n = 66): WW Arm 2 (n = 64): prednimustine (200 mg/m^2/d) Arm 3 (n = 63): interferon (5 mU for 3 mo)	3.75	Arm 1 versus arm 2. versus arm 3: FFT/FFTF: 24 versus 40 versus 35 mo (NS) 5-years OS: 78% versus 70% versus 84% (NS)
Ardeshna et al, 2003[42] BNLI	309	Arm 1 (n = 151): WW Arm 2 (n = 158): chlorambucil (10 mg/d)	16	Median OS (arm 1 vs. arm 2): 6.7 versus 5.9 years (NS)
Rituximab Era				
Ardeshna et al, 2014[46]	463	Arm 1 (n = 187): WW Arm 2 (n = 84): rituximab (375 mg/m^2/wk) (study arm was closed early) Arm 3 (n = 192): rituximab (375 mg/m^2/wk) + R-maintenance (every 2 mo for 2 years)	3.8	3-yr PNRNT (arm 1 vs. arm 2 vs. arm 3): 46% versus 78% versus 88% (arm 1 vs. arm 3 and arm 1 vs. arm 2: $P < .0001$; arm 2 vs. arm 3: P = NS) 3-years PFS (arm 1 vs. arm 2 vs. arm 3): 36% versus 60% versus 82% (arm 1 vs. arm 3: $P < .0001$; arm 2 vs. arm 3: $P = .011$; arm 1 vs. arm 2: $P = .0034$) 3-years OS (arm 1 vs. arm 2 vs. arm 3): 94% versus 96% versus 97%: P = NS between groups QoL: Arm 3 versus arm 1 superior Mental Adjustment to Cancer scale score ($P = .0004$), and Illness Coping Style score ($P = .0012$) between baseline and mo 7. Difference between arm 1 versus arm 2: P = NS
Kahl et al, ASH, 2011[45] ECOG abstract[a]	384	In patients responding to rituximab (375 mg/m^2/wk) induction (n = 274): Arm 1 (n = 140): R-maintenance (every 3 mo) Arm 2 (n = 134): R-retreatment at progression	3.8	TTF: 3.9 versus 3.6 years (NS) QoL: At 12 mo after randomization, no difference between arms

Abbreviations: ASH = American Society of Hematology; BNLI = British National Lymphoma Investigation; ECOG = Eastern Cooperative Oncology Group; FFT = freedom from treatment; FFTF = freedom from treatment failure; GELF = Groupe D'Etude des Lymphomes Folliculaires; NCI = National Cancer Institute; NS = not significant; OS = overall survival; PFS = progression-free survival; PNRNT = patients not receiving next therapy; ProMACE-MOPP = prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, procarbazine, and prednisone; QOL = quality of life; R-maintenance = rituximab maintenance; TNI = total nodal irradiation; TTF = time to treatment failure; WW = watch and wait.
[a]Included in abstract form because of potential importance of full final results that are not currently available.

Table 6 Criteria for Initiating Treatment of FL

Groupe pour l'Etude de Lymphome Folliculaire (GELF)[18,43]	Any of the following:[a] • A tumor >7 cm in diameter • 3 nodes in 3 distinct areas, each >3 cm in diameter • Symptomatic spleen enlargement >16 cm on CT • Organ compression • Ascites or pleural effusion • Presence of systematic symptoms • Serum lactate dehydrogenase or β2-microglobulin levels greater than normal • Hb value ≤100 g/L, neutrophil count ≤1.5 x 109/L, platelet count ≤100 x109/L
British National Lymphoma Investigation (BNLI)[42]	Any of the following: • B symptoms or pruritus • Rapid generalized disease progression in the preceding 3 mo • Marrow compromise (Hb value <100 g/L, WBC count <3.0 x 10^9/L, or platelet count <100 x 10^9/L) • Life-threatening organ involvement • Renal infiltration • Bone lesions • Macroscopic liver involvement

Abbreviations: CT = computed tomography; Hb = hemoglobin; WBC = white blood cell.
[a]Lactate dehydrogenase and β2 microglobulin within normal range were later added to GELF criteria.

Recommendation 3 (Level of Evidence: Category 2B). Ongoing randomized studies are examining early treatment with rituximab with or without rituximab maintenance in asymptomatic patients; 1 such study by Ardeshna et al (2014) has been published.[46] Should the positive outcome noted in the Ardeshna et al (2014) study be subsequently confirmed, early treatment with single-agent rituximab may change current practice based on its ability to substantially reduce the risk of relapse.

Question 3: What treatment options should be considered for symptomatic advanced-stage FL?

Background

International guidelines generally recommend the addition of rituximab to standard chemotherapy for the first-line treatment of FL, with no recommendation of one chemotherapy regimen over another.[16-20] Canadian provincial guidelines for the treatment of FL are available for Alberta and BC. The Alberta guidelines recommend giving 6 courses of bendamustine and rituximab (BR) or 6 to 8 courses of cyclophosphamide, vincristine, and prednisone (R-CVP), followed by 2 years of rituximab maintenance, with the preference being for BR as initial treatment given its increased PFS and lower toxicity.[21] The BCCA also recommends giving BR as a first-line treatment, followed by rituximab maintenance.[22]

Methodology

In comparing first-line regimens for the treatment of FL, we performed a literature search that included all phase III comparative studies. The following search terms were used: lymphoma, treatment, symptomatic, first-line, upfront, and untreated. The search included published randomized comparative studies only. In the chemoimmunotherapy combination section, only studies including rituximab-containing regimens were included.

Rituximab Monotherapy. Initially studied in relapsed or refractory FL, rituximab monotherapy administered weekly for 4 weeks produced a response rate of 48% and a median duration of response (DOR) of 13 months.[47] More recently, rituximab (375 mg/m^2 weekly for 4 weeks) followed by rituximab maintenance (375 mg/m^2 weekly for 4 weeks at 6-month intervals for a maximum of 4 courses or until progression) has been studied in untreated FL.[48] Complete restaging was performed at 6-month intervals before each scheduled maintenance course of rituximab. Restaging included physical examination, complete blood counts, chemistry profile, and repeated computed tomographic scanning of all areas of previous lymphoma involvement. Results demonstrated an ORR of 47% at 6 weeks, with an ORR after continued maintenance of 76% and a median PFS of 34 months.

Addition of Rituximab to Chemotherapy. Although the efficacy of rituximab was initially demonstrated as monotherapy, the main benefits of rituximab have been shown when combined with chemotherapy. Four randomized studies were identified comparing rituximab plus chemotherapy with chemotherapy alone (Table 7).[49-54] The use of chemoimmunotherapy produced ORRs of 81% to 96% and median remission duration of about 27 to 66 months. Although not supported in head-to-head studies, the response to chemoimmunotherapy appears to be superior to that of rituximab monotherapy.

In all studies, the addition of rituximab to chemotherapy significantly increased ORRs, with a difference between groups of 6% to 24% (Table 7). Additionally, rituximab significantly improved the DOR in all studies and improved OS in 3 of 4 studies. Based on the results of these randomized studies, it appears that the efficacy of chemoimmunotherapy is superior to that of chemotherapy alone.

Chemoimmunotherapy Combinations. Given the improvement in ORRs and DOR with the addition of rituximab to chemotherapy, only studies including rituximab-containing regimens were included in the literature search. A total of 3 phase III comparative studies were retrieved examining the first-line treatment of FL with chemoimmunotherapy (Table 8).[55-57]

A phase III study by Federico et al in 2013[55] compared the efficacy of 3 standard treatments: 8 doses of rituximab plus 6 cycles of R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), 8 doses of rituximab plus 8 cycles of R-CVP, and

Table 7 Phase III Studies Examining Rituximab Plus Chemotherapy versus Chemotherapy Alone in Untreated Advanced-Stage FL

Reference	N	Treatment	Median Follow-Up (years)	ORR	OS	Remission Duration
Bachy et al, 2013[49] Salles et al, 2008[54]	358	R-CHVP + IFN (n = 175) versus CHVP + IFN (n = 183)	8.3	94% versus 85% ($P < .001$)	8 years: 78.6% versus 69.8% ($P = .076$)	EFS: 8 years: 44.1% versus 27.9% Median: 5.5 versus 2.8 years ($P = .0004$)
Marcus et al, 2005, 2008[50,51]	321	R-CVP (n = 159) versus CVP (n = 162)	4.4	81% versus 57% ($P < .0001$)	4 years: 83% versus 77% ($P = .029$)	Median TTF: 27 versus 7 mo ($P < .0001$)
Hiddemann et al, 2005[52]	428	R-CHOP (n = 223) versus CHOP (n = 205)	1.5	96% versus 90% ($P = .011$)	2 years: 95% versus 90% ($P = .016$)	1.5 years TTF: 87% versus 70% ($P < .001$)
Herold et al, 2007[53]	358; 201 with FL	R-MCP (n = 105) versus MCP (n = 96)	4.1 versus 3.5	92% versus 75% ($P = .0009$)	4 years: 87% versus 74% ($P = .0096$)	4 years PFS: 71% versus 40% ($P < .0001$)

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CHVP = cyclophosphamide, Adriamycin, etoposide, prednisolone; CVP = cyclophosphamide, vincristine, prednisone; EFS = event-free survival; FL = follicular lymphoma; IFN = interferon; MCP = mitoxantrone, chlorambucil, prednisone; NG = not given; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R = rituximab; TTF = time to treatment failure.

8 doses of rituximab plus 6 cycles of fludarabine and mitoxantrone (R-FM) for the treatment of indolent lymphomas.[55] Three-year TTF and PFS were greater with R-CHOP and R-FM than with R-CVP ($P < .05$). In addition, R-CHOP demonstrated lower toxicity than R-FM, with a superior risk-benefit ratio (Table 8). Results of this study demonstrated that R-CHOP is an effective option for the treatment of FL.

Bendamustine is a cytotoxic bifunctional alkylating agent that is highly effective as monotherapy or when combined with rituximab in relapsed and refractory lymphoid malignancies.[35,58-60] Although bendamustine has been used for more than 20 years in Germany, it only gained approval for the management of lymphoid malignancies in the United States in 2008 and in the European Union in 2010, with approval in Canada in August 2012. Given the long-term experience with bendamustine in Germany, Rummel et al in 2013[56] compared the efficacy and safety of BR versus R-CHOP in patients with untreated indolent NHL and mantle cell lymphoma. Results of this phase III study demonstrated an improvement in the primary outcome and PFS in the BR group (FL subgroup: not reached (NR) vs. 40.9 months; HR = 0.61; $P = .0072$). There was also an improvement in the time to next treatment with BR compared with R-CHOP (NR vs. 42.3 months; HR = 0.52; $P < .0001$). Furthermore, the safety profile was improved with BR, with lower rates of alopecia, hematologic toxicity, and infections compared with R-CHOP; however, rates of skin reactions were increased ($P < .05$) (Table 8). The improved efficacy of BR versus R-CHOP, as well as lower toxicity, suggests BR should be the preferred treatment standard versus R-CHOP in FL.

To confirm results of the Rummel et al[56] study in North America, a phase III study (the BRIGHT study) examined the efficacy and safety of BR, R-CHOP, and R-CVP.[57] Results showed that the complete response/remission (CR) rate for BR is statistically noninferior to that of R-CHOP/R-CVP ($P = .0225$). Safety results show that all 3 treatment regimens have distinct toxicity profiles. Nausea, vomiting, and drug hypersensitivity occurred more frequently with BR, whereas constipation, neuropathy, and alopecia occurred more frequently with R-CHOP and R-CVP (Table 8). The BRIGHT study supports the results of the Rummel et al[56] study, demonstrating that BR is at least noninferior to R-CHOP/R-CVP. However, the use of CR rate is not an appropriate primary end point for efficacy in FL and is therefore a major weakness of the study.

Recommendation 1 (Level of Evidence: Category 2A). Chemoimmunotherapy should be used in preference to rituximab monotherapy for the first-line treatment of symptomatic advanced stage FL, except when chemotherapy is contraindicated, based on the observed lower response to rituximab monotherapy shown in clinical trials.

Recommendation 2 (Level of Evidence: Category 1). Given the improved ORR and PFS demonstrated with the addition of rituximab to a number of chemotherapy combinations, rituximab should be added to chemotherapy in the first-line treatment of symptomatic advanced-stage FL.

Recommendation 3 (Level of Evidence: Category 1). We currently recommend BR as the preferred chemoimmunotherapy for the first-line treatment of symptomatic advanced-stage FL given the superior efficacy and favorable tolerability of this regimen versus R-CHOP in 2 randomized trials. Based on high-level evidence, there is uniform consensus that the intervention is appropriate.

Question 4: In which patients should additional treatment be considered after first-line induction?

Background

To reduce the risk of relapse, additional strategies have been sought to either maintain or improve the initial response achieved with first-line induction therapy. The goal of maintenance therapy is to sustain the best initial response achieved with first-line induction, whereas consolidation therapy aims to improve the quality

Table 8 Phase III Comparative Chemoimmunotherapy Studies for First-Line Treatment of FL

Reference	Treatment	Patient Population	N	Median Follow-Up	Response Rates	OS	Remission Duration	Toxicity
Federico et al, 2013[55]	R-CVP versus R-CHOP versus R-FM; No maintenance treatment	Grade 1, 2, 3a FL; Ann Arbor stage II -IV; ECOG PS 0 - 2; active disease	R-CVP: 178 R-CHOP: 178 R-FM: 178	34 mo	ORR: 88% versus 93% versus 91%; $P = .247$	3 years: 95%	3-years TTF: 46% versus 62% versus 59%; R-CHOP versus R-CVP: $P = .003$; R-FM versus R-CVP: $P = .006$ 3-years PFS: 52% versus 68% versus 63%; $P = .011$	Grade 3/4 neutropenia (%): 28 versus 50 versus 64; $P < .001$ Second malignancies: 4 versus 5 versus 14 patients
Rummel et al, 2013[56]	BR versus R-CHOP; No Maintenance treatment	Age $\geq$18 years; WHO PS $\leq$ 2; Histologically confirmed MCL, iNHL (FL grades 1 and 2, Waldenstrom macroglobulinemia); small lymphocytic; and marginal-zone lymphoma	BR: 274 R-CHOP: 275	45 mo	ORR: 93% versus 91%; NS CR: 40% versus 30%; $P = .021$	43 versus 45 patients died; NS	Overall median PFS: 69.5 versus 31.2 months; HR = .58; $P < .0001$ Median PFS for FL: NR versus 40.9 mo; HR = 0.61; $P = .0072$ Median TTNT: NR versus 42.3 mo; HR = 0.52; $P < .0001$	All grades: Alopecia (%): 0 versus 100; $P < .0001$ Hematologic (%): 30 versus 68; $P < .0001$ Infections (%): 37 versus 50; $P = .0025$ Skin reactions (%): 16 versus 9; $P = .024$
Flinn et al, 2014[57] BRIGHT study	BR versus R-CHOP/ R-CVP; No maintenance treatment	Age $\geq$ 18 years; histologically confirmed CD20$^+$ iNHL or MCL; ECOG PS 0-2; Ann Arbor stage $\geq$ 2; adequate renal, hepatic, hematologic function	BR: 224 R-CHOP: 104 R-CVP: 119	NG	ORR: 97% versus 91%; Superiority: $P = .0102$ CR: 31% versus 25%; Noninferiority: $P = .0225$; Superiority: NS	NG	NG	All grades: BR versus R-CHOP; BR versus R-CVP: Nausea (%): 63 versus 58, NS; 63 versus 39, $P < .01$ Vomiting (%): 29 versus 13, $P < .01$; 25 versus 13, $P < .05$ Neuropathy (%): 9 versus 44, $P < .0001$; 14 versus 47, $P < .0001$ Alopecia (%): 4 versus 51, $P < .0001$; 3 versus 21, $P < .0001$ Infections (%): 55 versus 57, NS; 53 versus 50, NS

Abbreviations: BR = bendamustine and rituximab; CR = complete response; CRu = complete response unconfirmed; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; FL = follicular lymphoma; IFN = interferon; iNHL = indolent non-Hodgkin lymphoma; MCL = mantle cell lymphoma; MCP = mitoxantrone, chlorambucil, and prednisone; NG = not given; NS = not significant; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; R = rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, and prednisone; R-FM = rituximab, fludarabine, and mitoxantrone; TTF = time to treatment failure; TTNT = time to next treatment; WHO = World Health Organization.

of the response, preferably through eradication of minimal residual disease.[61]

Before rituximab, maintenance therapy using interferon was attempted; however, because of the introduction of rituximab, most guidelines recommend R-maintenance based on positive outcomes in phase III trials.[16-20] In Canada, the Alberta guidelines recommend giving R-maintenance every 3 months for a total of 2 years (375 mg/m^2 intravenous single dose every 3 months for a total of 8 doses) if a PR or CR was achieved after induction.[21] The BCCA also recommends giving rituximab as maintenance if at least a PR is achieved after induction.[22]

Radioimmunotherapy (RIT) and high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) are 2 types of consolidation strategies investigated in the first-line setting. With the exception of the NCCN guidelines, all European guidelines do not recommend RIT consolidation because there are insufficient data in patients receiving RIT consolidation after rituximab-containing induction therapy, as well as a lack of phase III trials comparing RIT consolidation with R-maintenance.[16-20] In terms of ASCT, all European guidelines strictly do not recommend ASCT in first-line therapy for FL outside of the clinical trials setting, and the NCCN guidelines do not even discuss ASCT for first-line therapy.[16-20] In Canada, none of the provincial guidelines available mention either RIT or ASCT consolidation in the first-line setting.[21,22]

Methodology

In examining maintenance treatment after first-line induction in FL, we performed a literature search of all phase III studies. The following search terms were used: follicular, lymphoma, and maintenance. Additionally, a literature search was performed to identify all phase III trials of consolidation therapy after first-line induction in FL. The following search terms were used: follicular, lymphoma, consolidation, radioimmunotherapy, transplantation, first line, initial, front line, and primary. Our literature search was restricted to published studies using rituximab plus chemotherapy as induction.

Maintenance Therapy. A total of 2 randomized studies have compared maintenance to observation after first-line treatment with rituximab plus chemotherapy in FL (Table 9).[62,63] Both studies gave R-maintenance, resulting in improved CR rates that ranged from 71.5% to 80%. The study by Salles et al in 2011 additionally reported an improved PFS of 74.9% at 3 years.[63] Although there was a numeric increase in PFS in the study by Vitolo et al, the difference between groups did not reach significance.[62] In the latter study, both treatment arms were given rituximab consolidation, which may explain the higher PFS shown in both groups.[62] Although the benefit of R-maintenance after BR was not examined in a phase III trial, R-maintenance has shown improvements in CR rates after a number of rituximab-based chemotherapies. It is

Table 9 Published Phase III Studies Examining Maintenance After First-Line Induction in FL

Reference	Treatment	N	Median Follow-Up	Maintenance Schedule	Patient Population	Efficacy	Safety
Vitolo et al, 2013[62]	R-FND + R-consolidation + R-maintenance (n = 101) versus observation (n = 101)	Total: 234; 202	34 mo	Consolidation: Rituximab once weekly for 4 wk Maintenance: For 8 mo, rituximab once every 2 mo for a total of 4 doses	Age: 60-75 years FL grade 1, grade 2, grade 3a Stage II, stage III, stage IV >50%, FLIPI ≥3	At 18 mo (3 mo after end of maintenance): Patients in CR/CRu: 87% versus 71%; $P = .006$ Converted from PR to CR/CRu: 60% versus 15%; $P = .008$ 2-years PFS: 81% versus 69%; HR = 0.74; $P = .226$ OS: NS between arms	Grade 3/4 neutropenia: 14% versus 1% Grade 3/4 infections: 3% versus 1%
Salles et al, 2011[63] PRIMA	Induction: R-CVP, R-CHOP, or R-FCM + R-maintenance (n = 505) versus observation (n = 513)	Total: 1217; ITT: 1018	36 mo	Single dose of rituximab every 2 mo for 2 years	Age >18 years FL grade 1, grade 2, grade 3a ECOG ≤2	At end of maintenance: CR/CRu: 71.5% versus 52.2%; $P = .0001$ Converted from PR to CR/CRu at 2 years: 52% versus 30%; $P = .0001$ 3-years PFS: 74.9% versus 57.6%; HR = 0.55; $P < .0001$ OS: NS between groups	Any AE: 56% versus 37%; $P < .0001$ Any grade 3/4 AE: 24% versus 17%; $P = .0026$ Grade 3/4 neutropenia: 4% versus 1% Grade 2-4 infections: 39% versus 24%; $P < .0001$ AEs leading to treatment discontinuation: 4% versus 2%; $P = .029$

Abbreviations: AE = adverse event; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CR = complete response; CRu = complete response unconfirmed; CVP = cyclophosphamide, vincristine, and prednisone; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; HR = hazard ratio; ITT = intention to treat; NS = not significant; OS = overall survival; PFS = progression-free survival; PR = partial response; R = rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-FCM = rituximab, fludarabine, cyclophosphamide, and mitoxantrone; R-FND = rituximab, fludarabine, mitoxantrone, and dexamethasone.

Table 10 Phase III Trials of High-Dose Therapy and Autologous Stem Cell Transplantation in the First-Line Setting

Reference	Treatment	N	Median Follow-Up (years)	OS	Duration of Response	Response Rates	Safety
Ladetto et al, 2008[89] **GITMO/IIL**	R-CHOP (comparator): • Initial: 6 courses CHOP followed by 4 infusions rituximab (375 mg/m^2) • If PR or PCR positivity at treatment cessation: 2 additional infusions of rituximab • Radiotherapy: 30-36 Gy on bulky sites or residual masses ~ 2 mo after treatment cessation R-HDS: • Initial: 2 courses of APO (doxorubicin 75 mg/m^2 on d 1 and d 22, vincristine 1.2 mg/m^2 on d 1 and d 15, and prednisone 50 mg/m^2 on d 1-22). If no CR, 2 courses of DHAP (cisplatin 100 mg/m^2 on d 1, cytarabine 4 g/m^2 on d 2, and dexamethasone 40 mg on d 1-4) • Mobilization: Etoposide (VP16) 2 g/m^2 and 2 courses of rituximab (375 mg/m^2). After 40 d, 7 g/m^2 cyclophosphamide, followed by in vivo purging with 2 courses of rituximab (375 mg/m^2) • HDT: mitoxantrone 60 mg/m^2 on d −5 and melphalan 180 mg/m^2 on d −2 • Radiotherapy: 30-36 Gy on bulky sites or residual masses ~ 2 mo after ASCT • If PR or PCR positivity at treatment cessation: 2 additional infusions of rituximab	134	4.25	R-CHOP versus R-HDS: 4 years: 80% versus 81%, $P = .96$	R-CHOP versus R-HDS: 4-years EFS: 28% versus 61%; $P < .001$ 4-years PFS: 31% versus 68%; $P < .001$ 4-years DFS: 45% versus 76%; $P < .001$	R-CHOP versus R-HDS: CR/CRu: 62% versus 85%; $P < .001$ PR: 8% versus 5% PD or SD: 30% versus 10%	TRM: R-CHOP: n = 1 R-HDS: n = 4 Secondary Malignancies: R-CHOP: MDS/AML, n = 1 (fatal); solid tumors, n = 3 R-HDS: MDS/AML, n = 5 (3 fatal); solid tumors, n = 1

Abbreviations: AML = acute myeloid leukemia; APO = doxorubicin, prednisone, and vincristine; ASCT = autologous stem cell transplantation; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; CR = complete response; CRu = unconfirmed complete response; DFS = disease-free survival; DHAP = dexamethasone, cytarabine, and cisplatin; EFS = event-free survival; FL = follicular lymphoma; GITMO = Gruppo Italiano Trapianto di Midollo Osseo; HDT = high dose therapy; IIL = Intergruppo Italiano Linfomi; MDS = myelodysplastic syndrome; OS = overall survival; PCR = polymerase chain reaction; PD = progressive disease; PFS = progression-free survival; PR = partial response; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HDS = rituximab-supplemented high-dose sequential chemotherapy with autografting; SD = stable disease; TRM = treatment-related mortality.

therefore reasonable to conclude that R-maintenance would also improve outcomes after first-line treatment with BR.

The addition of R-maintenance significantly increased the overall number of adverse events in both studies, with slightly higher rates of neutropenia and infections reported (Table 9). However, R-maintenance was generally well tolerated, with few patients withdrawing because of treatment-related toxicities.[63]

Maintenance Schedule. A number of maintenance schedules of rituximab have been used after treatment with rituximab plus chemotherapy in front-line and relapsed FL.[63-66] The duration of R-maintenance used in clinical trials has varied from a minimum of 2 courses of 4 doses per week to a maximum of 2 years or until disease progression. In addition, the frequency of treatment with rituximab varies in clinical trials and has been given every 2 months,[62,63] every 3 months,[64] every 6 months,[65] or 4 times weekly.[66] However, no randomized studies have compared the duration or frequency of R-maintenance after induction with rituximab plus chemotherapy.

Given the lack of head-to-head studies comparing the duration and frequency of R-maintenance, there is currently insufficient evidence to make recommendations on the maintenance schedule of rituximab.

Recommendation (Level of Evidence: Category 1). Given the improved response with R-maintenance versus observation in 2 randomized trials, maintenance rituximab is recommended after first-line treatment of FL.

Note: There is currently insufficient evidence to determine the optimal frequency and duration of maintenance rituximab after first-line treatment of FL.

Consolidation Therapy

Radioimmunotherapy

No published randomized studies were found examining the use of RIT after first-line therapy with only rituximab-based chemotherapy given as induction. However, 1 published randomized study included a subgroup of patients (n = 59 of 414) who were given rituximab-based chemotherapy as induction.[67,68] The study evaluated the efficacy and safety of consolidation with yttrium-90 (90Y)-ibritumomab tiuxetan in patients with advanced-stage FL. 90Y-ibritumomab tiuxetan consolidation significantly prolonged median PFS (after a median observation time of 3.5 years) in all patients (36.5 vs. 13.3 months; $P < .0001$), regardless of FLIPI subgroup. In addition, the final CR rate was 87%, and 77% of patients with partial response (PR) converted to complete response (CR)/complete response/remission unconfirmed (Cru). However, in the subgroup of patients given rituximab-based chemotherapy as induction, response improvement (conversion from PR to CR/CRu) was not significantly greater in the 90Y-ibritumomab tiuxetan consolidation arm (41.7% vs. 71.4%; $P = .34$). Given the small number of patients who had been given rituximab-based chemotherapy as induction, it is difficult to interpret the results of this study. There is therefore not sufficient evidence to currently support the use of this strategy after first-line treatment of FL.

HDT and ASCT

Only 1 published randomized trial comparing HDT and ASCT to conventional therapy after first-line treatment with rituximab-based chemotherapy was identified (Table 10).[69] In this study, 6 courses of R-CHOP were compared with rituximab-supplemented high-dose sequential chemotherapy with autografting (R-HDS) to assess the value of intensified chemotherapy as a first-line treatment for FL. After a median follow-up of 4.25 years, disease control and the 4-year event-free survival (EFS) were significantly improved in the R-HDS arm versus the R-CHOP arm (CR/CRu, 85% vs. 62%; 4-year EFS, 61% vs. 28%; $P < .001$ for both); however, there was no OS advantage of HDT with ASCT.[69] Secondary malignancies and treatment-related mortality were numerically higher in the R-HDS arm (Table 10). The cumulative incidence of myelodysplastic syndrome/acute myeloid leukemia at 4 years was 6.6% for R-HDS and 1.7% for R-CHOP ($P = .111$). For solid tumors, the cumulative incidence at 4 years was 1.5% for both arms.

Updated results were presented in abstract form at the 2013 annual meeting of the American Society of Hematology.[70] After a median follow-up of 9.5 years, the superior disease control achieved with R-HDS compared with R-CHOP was reaffirmed (CR, 83% vs. 57%; $P < .001$) but did not translate into either a 5- or 10-year OS advantage. Additionally, it was reported that achieving either a CR or molecular remission (MR) was associated with a significantly prolonged 10-year OS (CR vs. no CR, 80% vs. 43%; $P < .001$; MR vs. no MR: 83% vs. 57%; $P = .03$).

Recommendation (Level of Evidence: Category 1). We do not recommend HDT followed by ASCT as part of front-line treatment of FL given the lack of a survival benefit and the potential toxicity of this approach.

Note: There is no evidence to support the use of RIT after first-line treatment of FL.

Acknowledgments

The authors would like to acknowledge the financial support of Lymphoma Canada at all stages of the development of this guideline, including medical writing support provided by Anna Christofides and Marina Komolova of New Evidence.

Disclosure

The authors have stated that they have no conflicts of interest.

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