Published in final edited form as:

Community Oncol. 2012 November 1; 9(11): S53–S60. doi:10.1016/j.cmonc.2012.09.015.

Considerations in the initial management of follicular lymphoma

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Introduction

Follicular lymphoma (FL) is the most common indolent lymphoma and is the second most frequently occurring lymphoma in the western world, accounting for approximately 22% of B-cell lymphomas.^{1,2} The lymph nodes are the primary site of involvement, although patients frequently present with infiltration of the peripheral blood and bone marrow. On rare occasions, FL may involve other organs such as the gastrointestinal tract or the liver.^{3,4}

The disease mostly affects older adults with a median age of onset in the sixth decade.^{2,5} Approximately two-thirds of patients have advanced disease at diagnosis (stage III or IV), yet they may remain asymptomatic at presentation.² In contrast to more aggressive B-cell lymphomas, the presence of B symptoms (ie, fever [$>38^{\circ}\text{C}$], drenching night sweats, and weight loss [$>10\%$ body weight over 6 months]) and reduced performance status is uncommon in patients presenting with FL.⁶ Patients' prognosis at diagnosis and disease clinical course can be markedly variable, with some patients experiencing spontaneous remissions (approximately 2%–3%), while for others the disease may follow an aggressive clinical course.⁷ Although FL is sensitive to a variety of immunotherapy and chemotherapy agents, it exhibits a continuous pattern of relapses with decreasing sensitivity to treatment, and has a median survival that has traditionally been stated to be approximately 8 to 10 years.^{6,8} However, recent advances in therapy are changing expected outcomes.⁹

Histological grade 1 and 2 FL usually presents with an indolent disease course and is conventionally considered incurable, except in some patients who present with localized disease or those who undergo allogeneic stem cell transplantation. Grade 3 FL may follow a more aggressive clinical course and debate remains regarding the most appropriate regimens for these patients and whether the goal of treatment can be cure. Histological transformation from FL into a high-grade lymphoma is observed in approximately 3% of patients annually and is associated with a progressive clinical course, poor response to treatment, and shorter survival.^{10,11}

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Disclosures: Dr Nastoupil has received an honorarium from Hoffman-La Roche and is a consultant to Genentech/Roche. Ms Hirschey has nothing to disclose.

Dr Flowers is a consultant to Celgene, Clinical Care Options, Genentech/Roche (unpaid), Millennium/Takeda (unpaid), Prescription Solutions, Seattle Genetics, and Spectrum, and has received research funding from Abbott, Calistoga Pharmaceuticals, Celgene, Eastern Cooperative Oncology Group, Janssen Pharmaceutical, Memorial Sloan-Kettering Cancer Center, Millennium/Takeda, National Cancer Institute, National Institute of Health, Northwestern University, Southwest Oncology Group, and Spectrum.

Guidelines

Several guidelines exist for the diagnosis and management of FL including the prominently used guidelines from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO).^{12,13}

Diagnostic work-up

Patients with FL generally present to their physicians after they develop lymphadenopathy or other symptoms associated with FL. An excisional lymph node biopsy is essential for the classification of FL according to World Health Organization (WHO) criteria.^{9,14,15} FL cells appear as small cleaved cells and are usually associated with the specific genetic rearrangement of t(14;18)—often referred to as a hallmark of FL—which is present in almost 85% of cases of grade 1 and 2 FL.¹⁶ This translocation leads to the overexpression of the antiapoptotic protein BCL2, which is a molecular event that is vital to follicular lymphomagenesis. Biopsies should be histologically graded based on the number of centroblasts per high-power field using the most recent WHO classification.¹⁵ Immunophenotyping of the biopsied lymph node should be carried out to look for specific clusters of differentiation (CD) markers. The immunophenotype of FL is CD10, CD19, and CD20 positive, and CD5 negative. Fine-needle aspiration is currently being investigated as a less-invasive and more cost-effective option, but at present is not considered to be reliable for routine use.^{12,13,17}

Staging and risk assessment

Evaluation of patients suspected of having FL should include: a medical history and physical examination with assessment of performance status and evaluation of B symptoms; a complete blood cell count, HIV/hepatitis screen, electrolyte panel, renal and liver profiles, and blood chemistry (including lactate dehydrogenase levels); imaging such as a computed tomography (CT) scan of the neck, thorax, abdomen, and pelvis; and an excisional node biopsy with histologic analysis (Table 1).^{12,13} Debate exists surrounding the value of ¹⁸F-fluorodeoxyglucose positron-emission tomography (PET) scans in the diagnosis of FL, although PET may be recommended in selected cases.^{13,18,19} Patients should be staged according to the Ann Arbor staging system, which categorizes disease in 4 stages based on the location of tumors (Table 2).²⁰ Additional laboratory and imaging tests should be performed as appropriate.

The Follicular Lymphoma International Prognostic Index (FLIPI)—a prognostic assessment that combines the findings on 5 adverse prognostic factors—should be calculated to provide an indication of overall prognosis (Table 3).²² The total number of risk factors enables the patient to be placed into 1 of 3 risk groups: low risk (0–1 risk factor), intermediate risk (2 factors), or poor risk (≥ 3 adverse factors) with median 10-year survival times of approximately 71, 51, and 36 months, respectively, in the pre-rituximab era.²² FLIPI remains a useful prognostic index in patients treated in community practice according to an analysis by the National LymphoCare Study (NLCS).²³ An updated version of the FLIPI (FLIPI2) was developed in a prospective study using progression-free survival (PFS) as a surrogate for overall survival (OS).²⁴ Although the FLIPI2 provides a useful prognostic model for FL, this index utilizes β_2 -microglobulin—a laboratory value that may not be routinely collected in clinical practice. In addition to the FLIPI/FLIPI2, assessment according to Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria or British National Lymphoma Investigation (BNLI) criteria (Table 3) is recommended as these criteria can be used as an indication of when it is appropriate to initiate treatment in a patient undergoing a period of watchful waiting (Table 3).^{7,21}

First-line treatment

Treatment options depend on tumor stage and degree of tumor burden as assessed by GELF criteria. At present, FL is considered an indolent and usually incurable disease, therefore the goal of therapy is to extend the lives of patients and obtain adequate disease control to maintain a good quality of life. Patient characteristics—including daily functioning and comorbidities—should be taken into account when deciding the most appropriate course of action. Other considerations include researching available clinical trials for patients, which may address unanswered questions and may provide access to novel therapeutics. The initial publication of data from the NLCS indicated that among patients with FL diagnosed in the United States from 2004 through 2007, 6% received treatment on a clinical trial as part of initial therapy.²⁵ It is essential for the patient to be made aware of any and all treatment options, so that he or she will be able to make an informed and educated decision about therapy and have comfort and confidence in this decision.

Stage I and contiguous stage II

It is rare for patients to be diagnosed with localized disease, however, when such patients are encountered, a watchful waiting strategy can be considered based on the findings from a retrospective study which showed that these patients can continue for prolonged periods without requiring intervention.²⁶ This study investigated 43 patients with untreated stage I and II follicular small-cleaved and follicular mixed lymphoma for a median follow-up time of 86 months.²⁶ At 5, 10, 15, and 20 years, 97%, 85%, 58%, and 22% patients were alive, respectively.²⁶ At 5, 10, and 15 years, 76%, 56%, and 48% of patients, respectively, had not yet received treatment. The median overall time to treatment for the patient population was 7.8 years, with 21% transformation rate. Those with disease progression had a 22-month median time to treatment.

Localized external beam radiation therapy can also be considered for patients with early-stage, low tumor burden FL based on data suggesting that a proportion of these patients may achieve long-term disease-free survival with this approach.^{12,13} In general, local radiotherapy is delivered to the involved lymphoid region at a dose of 24–30 Gy with an additional 6 Gy administered in select cases, such as those with bulky or slowly regressing disease. Long-term follow-up in observational studies of patients with early-stage disease treated with radiotherapy shows 10-year OS rates of 60% to 80%, with 10-year relapse-free survival rates of 45% to 60%, and median survival of approximately 15 to 20 years.²⁷ These data suggest that a subset of patients with limited-stage FL may be cured with radiation alone.

Recent data from the NLCS concerning newly diagnosed stage I FL indicated that early outcomes for patients receiving radiation were similar to several other initial therapy options including chemoimmunotherapy and rituximab alone.²⁸ This suggests that other options are currently being used that may demonstrate similar long-term outcomes to radiation in the future. Patients with stage I/II FL with high tumor burden should be treated with systemic therapy as described below for stage II noncontiguous, stage III, and stage IV FL.¹³

Stage II non-contiguous, stage III, and stage IV FL

Watchful waiting—Two randomized trials comparing watchful waiting with immediate chemotherapy in asymptomatic advanced-stage low-grade B-cell non-Hodgkin lymphoma demonstrated no difference in OS for an initial chemotherapy strategy.^{7,21} In the first study, patients with newly diagnosed stage II–IV FL with a low tumor burden were randomly assigned to: no initial treatment; prednimustine 200 mg/m²/d for 5 days per month for 18 months; or interferon- α (IFN- α) 5 MU/d for 3 months followed by IFN- α 5 MU three times

per week for 15 months.²¹ The median treatment-free interval was 24 months for the untreated watchful waiting arm; the treatment failure-free interval was 40 months in the prednimustine arm and 35 months and in the IFN- α arm. The overall response to therapy, when deferred, was similar to the response rates with immediate chemotherapy. The median OS was not reached and the OS rates at 5 years were 78%, 70%, and 84% in the watchful waiting, prednimustine, and IFN- α arms, respectively. In the second study, patients with asymptomatic, advanced-stage, low-grade non-Hodgkin lymphomas were randomized to receive immediate systemic therapy with oral chlorambucil 10 mg/d continuously or to observation, with systemic therapy delayed until disease progression.⁷ The median length of follow-up was 16 years during which there were no differences in OS or cause-specific survival between the 2 groups.

Continual monitoring is an integral part of a watchful waiting strategy. The NCCN guidelines recommend performing a medical history, physical examination, and laboratory tests every 3 to 6 months for 5 years and then annually or as clinically indicated. A CT scan is indicated no more frequently than every 6 months during the first 2 years and then no more frequently than annually after 2 years.¹³ As there are not definitive randomized prospective data demonstrating the benefits of any interval for scans, individual patients should be involved in decision-making regarding the preferred surveillance approach, which should consider the risks and benefits of CT scans.²⁹

Rituximab monotherapy—Rituximab, a human chimeric unlabeled antibody to the CD20 antigen, has been in clinical use since it was approved in 1998. Rituximab is typically administered weekly for 4 weeks at a dose of 375 mg/m². Other than infusion-related toxicities, it is generally well tolerated. The primary issues are cost, and that rituximab, like chemotherapy, does not cure patients with advanced FL.

A prospective study of rituximab monotherapy in 36 patients with previously untreated, advanced-stage, asymptomatic grade 1 FL demonstrated an overall response rate of 72% with a 36% complete response (CR) rate. The median time to progression was 2.2 years.³⁰ Another study reported the long-term results of rituximab induction monotherapy in 46 patients with low tumor burden FL. Overall, 52% patients had a CR or unconfirmed CR; 28% had a partial response (PR); and 20% had stable or progressive disease. After 83.9 months of follow-up, the median PFS was 23.5 months and the OS rate was 91.7%.³¹

Two recent studies have shown that initial treatment with rituximab significantly delays the need for new therapy.^{32,33} In the first study, 462 patients with stage II, III, IV, asymptomatic, non-bulky FL (grade 1, 2, and 3a) were randomly assigned to: watchful waiting; rituximab 375 mg/m² weekly for 4 weeks; or rituximab 375 mg/m² weekly for 4 weeks followed by rituximab maintenance every 2 months for 2 years.³² At the Month 7 interim analysis, 9% of patients in the watchful waiting arm had responded (either remission or PR) while in the rituximab and rituximab plus maintenance arms, the response rates were 78% and 85%, respectively. At the time of the interim analysis 93 patients (20%) had initiated new treatment. Of note, the time to initiation of new therapy was significantly longer in both the rituximab arms compared with watchful waiting (both $P < .001$) and the median time was not reached at 4 years. Not surprisingly, there were significant differences in PFS between the watchful waiting and rituximab arms ($P < .001$ for each of rituximab arms vs watchful waiting).

In the second study, 384 patients with FL and low tumor burden received either: Schedule 1, initial rituximab treatment (375 mg/m²/wk for 4 weeks) followed (in responders) by maintenance with a single dose of rituximab administered every 3 months; or Schedule 2, initial rituximab treatment (375 mg/m²/wk for 4 weeks) followed (in responders) by

rituximab 375 mg/m² weekly for 4 weeks administered on disease progression. Follow-up showed that both strategies delayed the time to initiation of cytotoxic therapy (time to treatment failure of 3.9 years for Schedule 1 versus 3.6 years for Schedule 2) compared with historical data for watchful waiting strategies in similarly defined populations.³³

Based on the findings from these studies, rituximab, as a brief course with or without ongoing maintenance, can be considered as an option for low tumor burden FL. At present, however, rituximab monotherapy is not recommended in the guidelines.³⁴ Additional strategies are under development for antibody use alone or in combination with chemotherapy.³⁵

Rituximab plus chemotherapy—In general, indications for more aggressive treatment include the presence of any of the BNLI or GELF criteria, although some trials and clinicians have raised the possibility of using a high-risk FLIPI score as an indication for a more aggressive initial approach.^{13,22} The optimal treatment approach for patients with advanced stage FL remains controversial.³⁶ In previously untreated symptomatic patients with FL, standard induction treatment options include rituximab plus bendamustine (BR) or combination chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), cyclophosphamide, vincristine, and prednisone (CVP), or a fludarabine-containing regimen such as fludarabine, mitoxantrone, and dexamethasone (FND) or fludarabine and mitoxantrone (FM).¹³ Chemotherapy is not indicated alone, as trials that have compared chemotherapy regimens (CHOP or CVP) against chemotherapy combined with rituximab (rituximab plus CHOP [R-CHOP] or rituximab plus CVP [R-CVP]) have consistently shown that rituximab improves patient outcomes.^{37,38}

At present there is no consensus on the initial choice of chemotherapy to be used in combination with rituximab (Table 4).¹³ Data from the NLCS, a secondary analysis of the PRIMA study, and a randomized comparison of R-CVP, R-CHOP, and rituximab plus FM (R-FM) for previously untreated patients with advanced stage FL, have suggested that R-CHOP may result in somewhat better outcomes than other commonly prescribed rituximab chemotherapy regimens.³⁹⁻⁴¹ To date, the currently available data have not been sufficiently compelling to lead to firm recommendations. Preliminary data from a randomized phase III trial comparing R-CHOP with BR in previously untreated follicular, indolent, and mantle cell lymphomas showed that patients in the BR arm achieved a significantly better CR rate ($P = .0323$) and PFS ($P = .0002$) compared with R-CHOP.^{42,43} Of particular interest was the better short-term toxicity profile in patients treated with BR. BR was associated with significantly less grade 3/4 neutropenia and grade 3/4 leukocytopenia compared with R-CHOP (both $P < .0001$). Furthermore the BR regimen was associated with a markedly lower rate of alopecia (15%), which was of grade 1 severity only, compared with R-CHOP (62%). The only adverse event observed more frequently with BR than R-CHOP was drug-associated erythematous skin reaction. Radioimmunotherapy is also included as a first-line option in the NCCN guidelines based on data from a small trial of patients with stage III or IV FL who received a single 1-week course of ¹³¹I-tositumomab therapy as initial treatment.^{13,44} After a median follow-up of 5.1 years, the 5-year PFS for all patients was 59% and the median PFS was 6.1 years. For older or infirm patients unable to tolerate standard first-line therapy, the NCCN recommends radioimmunotherapy, rituximab monotherapy, or single-agent alkylators with or without rituximab.¹³ As front-line treatment, BR has also been suggested as a good option in this patient group given its improved tolerability profile compared with R-CHOP.⁴⁵

Maintenance therapy

Rituximab has shown remarkable efficacy in prolonging the duration of remission achieved with induction therapy.⁴⁶⁻⁵² In the PRIMA trial, 1019 patients with untreated FL who achieved a CR or PR following induction with rituximab and chemotherapy were randomized to rituximab maintenance every 8 weeks for 2 years or to observation. Active maintenance treatment improved the proportions of patients in complete remission and those progression-free at 3 years median follow-up but produced no differences in OS.⁴¹ The benefit of rituximab maintenance has been confirmed in a systematic review/meta-analysis of randomized trials.^{53,54} Alternative approaches to maintenance exist. Consolidation with yttrium-90 ⁹⁰Y-ibritumomab tiuxetan has also been found to prolong PFS in a phase III trial of 414 patients with advanced stage FL in first remission.⁵⁵ A meta-analysis of eight trials involving 1563 patients found some evidence that maintenance IFN improved PFS in FL, but there was no evidence for an OS benefit.⁵⁶ This treatment approach was, however, associated with significant toxicities that may have had a major impact on patients' quality of life.

Assessment of treatment response

Radiologic tests should be performed midterm and after completion of chemotherapy, and patients with insufficient or no response should be evaluated for early salvage regimens. A growing body of data suggests that a PET-CT scan is an effective means to evaluate response quality; however, this approach remains investigational in this disease until future study confirms its predictive value.⁵⁷ Studies have also indicated that assessment of minimal residual disease at the end of the treatment has some prognostic impact, but at present these data should not guide therapeutic strategies outside of clinical studies.⁵⁸

Follow-up

The ESMO and NCCN guidelines recommend that a medical history be taken and a physical examination be conducted every 3 to 6 months for 2 to 5 years, and subsequently once a year unless clinically indicated.^{12,13} Imaging evaluations are recommended every 6 months for 2 years and annually thereafter.

Conclusions

The availability of anti-CD20 monoclonal antibodies has led to significant improvements in the clinical outcome of patients with FL. Previously, the median survival of patients with FL was 10 years after diagnosis but patient survival has been extended in the last few decades.⁹ Despite these rapid advances, FL remains incurable for the majority of patients. For a small subset of patients with localized FL, radiation therapy may be curative, but this approach may be challenged by alternatives that are now available with the advent of rituximab and rituximab combinations that are well tolerated and with the emergence of active oral agents on the horizon. For the vast majority of patients who present with advanced-stage disease and are asymptomatic, watchful waiting remains an appropriate strategy, particularly for elderly patients. However, this axiom is also being challenged by trials demonstrating the PFS benefits of rituximab with limited toxicity. The decision to start chemotherapy should be based on the presence of B symptoms, vital organ compromise, performance status, and significant disease progression or transformation. It is important to discuss quality of life issues, chemotherapy-related side effects, and the risk of secondary malignancies with patients when making treatment decisions. Combined chemoimmunotherapy is an excellent option for patients who require therapy, although patients with significant comorbidities may benefit from less-intensive approaches. A proportion of patients does not respond to or become refractory to rituximab-containing therapy. New monoclonal antibodies and a

variety of novel targeted agents are under development and trials studying prognostic biomarkers are ongoing. For this reason, patients with newly diagnosed or relapsed/refractory FL should be encouraged to enroll in clinical trials.

Acknowledgments

Medical writing support was provided by Lucy Kanan of Anthemis Consulting Ltd, funded by Teva Branded Pharmaceutical Products R&D, Inc., Frazer, PA. The authors were not compensated and retained full editorial control over the content of the paper.

Dr Sinha has received research funding from Celgene.

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TABLE 1

Diagnostic workup for follicular lymphoma

Test	Details
Medical history and physical exam	Examination of node-bearing areas Examination of liver and spleen Assessment of performance status Evaluation of B symptoms (fever sweats, weight loss)
Laboratory tests	Complete blood cell count, differential, platelets HIV/hepatitis screen Electrolyte panel Renal and liver profiles Blood chemistries (including lactate dehydrogenase levels) Pregnancy testing in women of child-bearing age
Imaging	Computed tomography scan of the neck, thorax, abdomen and pelvis ¹⁸ F-fluorodeoxyglucose positron emission tomography in selected cases
Excision node biopsy	Histologic grading Immunophenotyping with immunohistochemical analysis and cytogenetic analysis if considered appropriate

TABLE 2Ann Arbor classification²⁰

Stage	Features
I	NHL is limited to 1 lymph node group (eg, neck, underarm, groin) above or below the diaphragm, or NHL is in an organ or site other than the lymph nodes (extranodal) but has not spread to other organs or lymph nodes
II	NHL is limited to 2 lymph node groups on the same side of the diaphragm, or NHL is limited to 1 extranodal organ and has spread to 1 lymph node groups on the same side of the diaphragm
III	NHL is in 2 lymph node groups, with/without partial involvement of an extranodal organ or site above and below the diaphragm
IV	NHL is extensive (diffuse) in 1 organ or site, with/without NHL in distant lymph nodes
For all stages	
A	No symptoms
B	Fever (>38°C), drenching night sweats, weight loss (10% body weight over 6 months)
For stages I–III	
E	Involvement of a single extranodal site contiguous or proximal to known nodal site

Abbreviation: NHL: non-Hodgkin lymphoma.

TABLE 3Prognostic assessments^{7,21,22}

GELF criteria	<ul style="list-style-type: none"> • Involvement of at least 3 nodal sites (each with a diameter >3 cm) <ul style="list-style-type: none"> o a nodal or extranodal mass > 7 cm in its greater diameter o or B symptoms o or splenic enlargement o or pleural/peritoneal effusion o or increased lactate dehydrogenase o or β_2-microglobulinemia • Cytopenias (leukocytes $<1.0 \times 10^9/L$ and/or platelets $<100 \times 10^9/L$) • Leukemia ($>5.0 \times 10^9/L$ malignant cells)
BNLI criteria	<ul style="list-style-type: none"> • Rapid, generalized disease progression in the preceding 3 months • Life-threatening organ involvement • Renal infiltration • Bone lesions • Presence of systemic symptoms: hemoglobin <10 g/dL or WBC $<1.5 \times 10^9/L$, or platelet counts $<100 \times 10^9/L$; related to bone marrow involvement
FLIPI Low risk = 1 factor Intermediate risk=2 factors High risk=3 factors	<ul style="list-style-type: none"> • Age >60 years • Serum lactate dehydrogenase level elevated • Hemoglobin level <12 g/dL • Number of nodal areas >4 • Ann Arbor stage III or IV disease

Abbreviations: BNLI, British National Lymphoma Investigation; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; WBC, white blood cell.

TABLE 4

Suggested regimens for first-line therapy in stage II non-contiguous, stage III, and stage IV FL follicular lymphoma if treatment is indicated¹³

Indication	Therapy
First line	Rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) Rituximab + cyclophosphamide, vincristine, and prednisone (R-CVP) Rituximab + bendamustine (BR) Rituximab + fludarabine containing regimen Radioimmunotherapy ^a
Elderly/infirm	Rituximab ^a Single-agent alkylators ± rituximab Radioimmunotherapy ^a
Maintenance	Rituximab

^aNot indicated as first-line treatment.