Where to start? Upfront therapy for follicular lymphoma in 2018

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The initial approach to the management of follicular lymphoma (FL) is challenging for patients and physicians. Most FL patients present with minimal symptoms; given the lack of a survival benefit to early treatment in this population, a period of observation without therapy is often appropriate. Once there is disease progression beyond low-tumor-burden criteria or symptoms prompting intervention, patients may be considered for an array of potential treatment options. These range from single-agent rituximab (anti-CD20) to various forms of chemoimmunotherapy, including rituximab or the newer anti-CD20 monoclonal antibody obinutuzumab. Unfortunately, prognostic and other clinical factors are of limited value in guiding optimal selection of therapy. Once patients complete initial treatment and achieve a complete or a partial remission, the next decision relates to the pros and cons of maintenance anti-CD20 therapy. Maintenance antibody administration can improve progression-free, but not overall, survival; hence, patient preferences typically drive this decision. Monitoring after remission is achieved should generally be guided by symptoms, physical examination, and laboratory findings, with routine surveillance imaging discouraged in the absence of new clinical issues. Given the wide range of options available and the importance of optimizing quality of life in this chronic health condition, education and shared decision making are pillars in the upfront management of FL to help patients achieve the best possible outcomes.

Learning Objectives

- Recognize prognostic factors for follicular lymphoma that stratify patients into groups based on expected survival
- Evaluate current initial management options in patients with follicular lymphoma

Introduction

Follicular lymphoma (FL) is the most common form of indolent non-Hodgkin lymphoma (NHL), accounting for ~20% of NHL cases globally and ~14 000 cases diagnosed annually in the United States.[1] FL is characterized by heterogeneous clinical presentations and outcomes. Generally, FL is considered incurable, despite improvements in survival observed over the past few decades internationally.[2-5] Now, most patients can anticipate a normal life expectancy, despite a diagnosis of FL.[6] The varied presentation at diagnosis and frequent lack of significant symptoms result in stark differences in initial management strategies, from observation to chemoimmunotherapy.

For most patients, FL is a slow-growing tumor that has an indolent behavior and allows an initial period of observation, followed by favorable response to initial therapy. Like other indolent lymphoid malignancies, immediate initial treatment is not required or recommended for many patients with FL who are asymptomatic at diagnosis and do not meet of any of the Groupe d'Etude des Lymphomes Folliculaires criteria for high (vs low) tumor burden. These include B symptoms; any nodal or extranodal tumor mass with a diameter $\geq$ 7 cm; involvement of $\geq$3 lymph nodes, each with a diameter $\geq$ 3 cm; pleural effusions or ascites; splenomegaly; white blood cell count $<$ 1000/mL; platelet count $<$ 100 000/mL; or circulating malignant cells ($>$5.0/mL).[7] The most widely used FL risk-stratification model has been the FL International Prognostic Index (FLIPI), which includes age, stage, hemoglobin level, number of nodal areas, and serum lactate dehydrogenase levels.[8] In a large national cohort study of FL patients managed in the United States, FLIPI risk groups were significant predictors of overall survival (OS) and progression-free survival (PFS) for patients who underwent initial management with observation, chemotherapy alone, rituximab (R) alone, or R-combination chemotherapy (R-chemotherapy).[9] The FLIPI-2 scoring system has also been proposed based on data demonstrating that β2-microglobulin greater than the upper limit of normal, longest diameter of the largest involved node $>$6 cm, bone marrow involvement, hemoglobin $<$ 12 g/dL, and age $>$ 60 years

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were factors independently predictive for PFS among 1093 patients with a newly diagnosed FL.[10] More recently, a simplified model including only the presence of bone marrow involvement and β2-microglobulin was found to predict PFS in patients treated with initial chemoimmunotherapy.[11] Gene expression and mutation-based approaches have integrated clinical and biological data in newer prognostic models.[12-14] This evolution of risk stratification using technological advances in DNA sequencing has yet to be implemented into clinical practice, and none of these prognostic models provides guidance for initial management.

Because of heterogeneous approaches and variable disease courses, management of FL affords one of the best opportunities to personalize therapy, with consideration of each treatment decision along the entire disease continuum. Given the variety of treatment options for FL, establishing factors that predict outcomes and developing strategies that balance toxicity and efficacy remain unmet research needs. Significant variability exists in the frontline management of FL. Commonly used options include watchful waiting (observation), the single-agent anti-CD20 antibody R, R with chemotherapy, or, more recently, the newer anti-CD20 obinutuzumab (O) with chemotherapy. For limited-stage disease (although uncommon), radiation is considered by some to be a potentially curative option. Initial treatment decisions often depend upon patient age, performance status, stage, and goals of care.[15] Although PFS is the most commonly used end point for clinical trials comparing different regimens,[16] PFS is limited as a marker of clinical benefit. Given that most patients with FL will not die of disease and have a survival comparable to age-matched controls,[6] achieving and maintaining optimal quality of life (despite disease- and treatment-related toxicity) is the principal goal of therapy. Unfortunately, quality-of-life measurements are not robust and specific enough for the FL disease setting to truly guide patients and clinicians in choice of therapy. In most cases, the range of therapeutic options is discussed with the patient; through shared decision making, a regimen is usually selected based on perceptions of preferences and goals of treatment.

Management of patients with low tumor burden

A key study in validating the role of "watch and wait" as an initial management strategy in FL is that of Ardeshna et al, which was published in 2003.[17] This trial randomized 309 subjects with advanced-stage, yet asymptomatic, FL to immediate treatment with oral chlorambucil vs delayed treatment when progression necessitated intervention. With a median follow-up of 16 years, there was no difference in OS, and, at 10 years, the chance of not requiring chemotherapy at all was nearly 20%. Given that single-agent chlorambucil is not commonly used any longer in FL, an important follow-up study was published in 2014 using R as primary management.[18] In this trial, 379 asymptomatic subjects with low-tumor-burden FL were randomized (1:1:1) to observation, R weekly for 4 weeks, or R weekly for 4 weeks and then once every 2 months for 2 years. About 3 years after the start of the trial, the R induction (without maintenance) arm was closed. With a median follow-up ~ 4 years, OS and rates of histologic transformation were similar between the approaches. Twelve percent of subjects in the observation arm were noted to have spontaneous regressions during the observation period. During the monitoring period, 56% of subjects in the observation group went on to receive their first treatment, whereas 17% of subjects in the maintenance group required additional (second) treatment. Interestingly, some measures of quality of life improved in all patients, suggesting that, with education and support, some aspects of psychological adaptation to the diagnosis occur in many patients, regardless of the management approach. This study provided rationale for single-agent R as an option for patients with newly diagnosed asymptomatic FL, although the lack of a survival benefit indicates that "watchful waiting" remains an appropriate approach for many patients.

In those low-tumor-burden indolent NHL patients who opt to receive single-agent R, the role of maintenance is an important issue. The RESORT trial treated 289 FL subjects with low-tumor-burden FL with 4 doses of weekly R and then randomized responding patients to maintenance R (1 dose every 13 weeks until progression) vs retreatment with R only at progression.[19] With a median follow-up of 4.5 years, the time to treatment failure was similar in both arms (~4 years), and >80% of patients had not required any cytotoxic therapy. No difference in health-related quality of life was seen.[20] Notably, these similar clinical outcomes were demonstrated with fewer total doses of R (median, 4 vs 18 doses) in those patients treated without maintenance. These data indicate that, if single-agent R is used as initial therapy, maintenance R is unnecessary, given the minimal clinical benefit and increased time, cost, and resource allocation, associated with its use.

Chemotherapy-based approaches are also frequently considered in both low- and higher-tumor-burden FL patients. A common clinical discussion includes the increased toxicity, at least in the short term, of a chemoimmunotherapy strategy vs the potential value of a longer remission. In a patient with low tumor burden but symptoms or other factors necessitating treatment, the decision to use a less intensive approach (eg, single-agent R) vs a more intensive approach (chemoimmunotherapy) remains highly subjective. In the absence of a clearly demonstrated long-term OS benefit, either strategy may be preferred by some patients or physicians. Additionally, the quality-of-life differences between less treatment-related toxicity vs longer disease control remain poorly defined. Presently, the best recommendation remains a detailed discussion of pros and cons of options for a given situation and efforts to allow patients to share in the decision-making process based on their personal preferences.

Management of patients with high tumor burden

Those patients with disease characteristics associated with high tumor burden (and meeting Groupe d'Etude des Lymphomes Folliculaires criteria described previously) are commonly treated with chemoimmunotherapy (Table 1). Although single-agent R may be considered in some cases, combination treatment would generally be expected to result in a deeper and longer response. Chemotherapy regimens, such as CVP (cyclophosphamide, vincristine, prednisone), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), and fludarabine (alone or with mitoxantrone) became widely combined

Table 1. Selected regimens for initial treatment of patients with high-tumor-burden FL

Regimen	References
R-chemotherapy without R maintenance	23,24
R-CHOP, R-CVP, R-bendamustine	
R-chemotherapy with R maintenance	25,27
R-CHOP, R-CVP, R-bendamustine	
O-combination chemotherapy with O maintenance	27
O-CHOP, O-CVP, O-bendamustine	
R + lenalidomide with R maintenance	33

with an anti-CD20 antibody, typically R.[21] Although these regimens have modest differences in PFS and similar rates of OS, their distinct toxicity profiles allow flexibility among the choice of chemoimmunotherapy. It is important to note that, at the time of treatment selection in FL, some consideration should always be given to the possibility of histologic transformation. Elevated lactate dehydrogenase level and high standardized uptake value on fluorodeoxyglucose–positron emission tomography scanning may suggest transformation from FL to diffuse large B-cell lymphoma[22] and should prompt at least consideration of a biopsy or use of R-CHOP or another anthracycline-containing regimen to "cover" for the possibility of an underlying aggressive histology or even "double-hit" (c-myc and bcl-2) translocations.[23]

In FL patients without evidence of histologic transformation, bendamustine has become an important agent when therapy is required.[24] Rummel et al randomized patients with advanced-stage untreated indolent and mantle cell lymphoma to bendamustine plus rituximab (B-R) vs R-CHOP in a prospective study. Use of B-R improved PFS in the study population, and this advantage was also noted in the FL subgroup of patients. B-R treatment had a greater risk for mucocutaneous reactions, but its lower rate of alopecia, cytopenias, and infection have led many to adopt it as a preferred initial therapy for FL. Of note, patients with grade 3A FL were excluded from this trial; although some investigators feel that B-R is reasonable treatment for this histological subset, this remains to be definitively established. The BRIGHT study also evaluated B-R in comparison with R-CHOP and R-CVP as upfront treatment for indolent and mantle cell lymphoma, and these data also suggest that B-R is at least noninferior.[25]

The role of maintenance therapy

The value of maintenance R after R-chemotherapy remains a debatable issue. The PRIMA study randomized 1019 patients in complete or partial remission after R-chemotherapy (R-CHOP, R-CVP, or R-FCM [fludarabine/cyclophosphamide/mitoxantrone]) to observation or 1 dose of R every 8 weeks for 2 years.[26] Improvements in PFS were noted in the R maintenance group at a median follow-up of 36 months (74.9% vs 57.6%); however, no difference in OS was demonstrated, even with longer follow-up. Grade 3 and 4 adverse events (principally infections) were increased in the R maintenance group (24% vs 17%), with symptoms and quality of life similar between the 2 arms.[27] This study suggests that the value of maintenance R after R-chemotherapy is primarily evident in the prolongation of remission, but that such is not associated with a clear survival or quality of life benefit. Given that retreatment with R when needed at relapse (as in the RESORT study) is another reasonable option, the use of maintenance R in this setting is variable. Furthermore, definitive data on the role of R maintenance after B-R are lacking.

The GALLIUM study evaluated the use of O, a glycoengineered type II anti-CD20 antibody (with greater antibody-dependent cellular cytotoxicity and direct B-cell killing than R), as initial therapy for FL.[28] A total of 1202 subject with untreated FL and indications for therapy were randomized to R-chemotherapy versus O-combination chemotherapy, followed by 2 years of R or O maintenance. Fifty-seven percent of subjects received bendamustine, with the remainder receiving CHOP or CVP as the chemotherapy backbone. Three-year PFS was 80% (O-combination chemotherapy/O maintenance) vs 73% (R-chemotherapy/R maintenance), with no differences in OS. Grades 3 to 5 adverse events (74.6 vs 67.8%) and serious adverse events (46.1 vs 39.9%), particularly infusion-related events, were more common in the O arm. Additional analyses have suggested that patients treated with bendamustine-based chemoimmunotherapy in this study demonstrated a relatively increased risk for severe infections and secondary neoplasms, although this finding is confounded by nonrandom chemotherapy assignment in the study.[29] The lack of a survival benefit in this trial, the potential for increased toxicity (possibly connected, in part, with bendamustine use), and the requirement for maintenance therapy may have limited the adoption of O by some clinicians as part of initial FL treatment. R and O remain reasonable options as part of an upfront chemoimmunotherapy strategy for FL.

Various investigators have pursued the possibility of a "chemotherapy-free" approach to FL. The concept, in theory, is to advance a treatment that could have greater efficacy than single-agent R but avoids the short- and long-term toxicity of chemotherapy. This approach has been advanced by several groups, including the Lymphoma Committee of the Alliance for Clinical Trials in Oncology, which conducted noncomparative trials of initial therapy using R plus galiximab (anti-CD80), R plus epratuzumab (anti-CD20), or R plus the immunomodulatory agent lenalidomide (R-lenalidomide).[29,30-32] Fowler et al at the MD Anderson Cancer Center conducted a phase 2 trial of R-lenalidomide in patients with untreated indolent lymphoma.[33] A 90% overall response rate was demonstrated, with 63% complete responses. The most common adverse events included neutropenia, muscle pain, and rash. To assess whether an approach using a novel agent plus R could be superior to chemoimmunotherapy, the phase 3 RELEVANCE study was conducted, and the results were presented recently.[34] In this study, 1030 subjects with high-tumor-burden FL were randomized to R-chemotherapy (mostly R-CHOP was used) with R maintenance vs R-lenalidomide with R maintenance. The primary objective was to establish superiority of the novel regimen, which was not achieved. Efficacy was similar with respect to overall response rates and PFS, regardless of the risk profile. R-chemotherapy was associated with more frequent grade 3/4 cytopenias and febrile neutropenia, whereas R-lenalidomide more commonly resulted in rash.

These findings suggest that, with similar efficacy, although with different cost and side effect profiles, R-chemotherapy and R-lenalidomide may be therapeutic options for consideration by lymphoma patients. The potential quality-of-life differences, if any, between the 2 approaches remain to be clarified.

Conclusions

Despite advances in the understanding of FL biology and prognosis, initial treatment largely remains defined by patient preferences and clinical judgment. A "watch and wait" approach in low-tumor-burden patients without symptoms remains appropriate. When therapy is needed, a course of single-agent R can be considered and can result in durable remissions for some patients. When a higher tumor burden is present, or when a low-tumor-burden patient accepts greater toxicity in exchange for a longer remission, chemoimmunotherapy is appropriate with either bendamustine or CHOP as a backbone. The value of O (vs R) and postinduction maintenance (vs observation) appears to be relatively modest. The substitution of lenalidomide for chemotherapy in combination with R is associated with comparable (but not superior) efficacy, although it is associated with distinct toxicity. Ongoing research is focused on efforts to determine which FL patients are likely to die of disease (to improve survival with novel approaches), whereas the majority (who will die with disease) need better tools and approaches to use regimens that can best improve and sustain optimal quality of life. In the meantime,

patient education and collaboration in treatment selection remain central to the clinical care of patients with FL.

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