Published in final edited form as:

Int J Hematol Oncol. 2012 October ; 1(1): 35–45. doi:10.2217/ijh.12.7.

Initial management strategies for follicular lymphoma

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SUMMARY

Follicular lymphoma (FL) can vary markedly in its initial presentation, and no single standard approach for its initial management has been adopted. Available options for the initial management of FL include watchful waiting, radiation, single-agent rituximab and combination of rituximab and chemotherapy with strategies segregated for patients who have low and high tumor burden disease based on established criteria. However, marked debate occurs regarding the role of watchful waiting in the modern era for low tumor burden, asymptomatic patients, the optimal timing of rituximab, the selection of chemotherapy regimen to partner with rituximab in high tumor burden patients, and strategies for the management of relapsed disease. We provide an evidence-based discussion on these and other issues regarding the management of FL, and propose a mathematical modeling approach for addressing some of these questions.

Non-Hodgkin's lymphoma (NHL) is the seventh most common cancer diagnosis in the USA, and represents a heterogeneous group of malignant lymphoid diseases that vary significantly in their biological and clinical behaviors. The American Cancer Society estimates that in 2012 there will be 70,130 incident cases of NHL, and 18,940 deaths associated with NHL [1]. Worldwide, greater than 200,000 individuals are affected by a new diagnosis of NHL annually. Follicular lymphoma (FL) is the second most frequent lymphoma subtype worldwide, with an increasing incidence in the western world over the last two decades. Many patients are asymptomatic at presentation, while others may exhibit B symptoms, such as weight loss, fevers and night sweats. Most patients present with advanced-stage disease (stage III or IV) at diagnosis. Available options for the initial management of FL include watchful waiting (WW; or initial active observation), radiotherapy, immunotherapy, single-agent chemotherapy, and combination chemotherapy. An initial publication from the NLCS trial indicated that in clinical practice a wide range of management strategies are used and no single standard approach for the initial management of FL in the USA has been adopted [2]. Among more than 2700 patients enrolled at 265 sites, the initial strategy was: WW in 17.7%, rituximab monotherapy in 13.9%, a clinical trial in 6.1%, radiation therapy in 5.6%, chemotherapy in 3.2% and rituximab with chemotherapy in 51.9%. A current strategy for the initial management of patients with FL is shown in Figure 1. Systematic approaches for comparing the benefits of various

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Financial & competing interests disclosure The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

management strategies are needed to address this clinical scenario where randomized comparisons of these approaches are unavailable or will not be possible in a timely fashion.

Initial management strategies for FL

Although uncommon, early-stage (I/II) FL patients have typically been managed with involved field radiotherapy owing to the possibility of cure. This approach has been based on the findings that relapse after 10 years was rare in observations from British National Lymphoma Investigation (BNLI) [3] and MD Anderson studies [4]. However, emerging data on practice patterns for FL in the USA raise the possibility that other strategies for managing patients with localized disease may also be employed [5].

Advanced-stage FL is commonly divided into groups of patients who have low tumor burden or high tumor burden based on defined criteria (Box 1).

Among low tumor burden advanced-stage FL patients, deferring initial chemotherapy treatment has been supported by the following concerns: treatment would result in side effects impairing patients' quality of life, cumulative courses of therapy might affect the feasibility of subsequent lines of treatment at relapse or transformation, and no meaningful clinical benefit arises from immediate treatment compared with the WW strategy [6–9]. For patients undergoing WW, the initiation of treatment is triggered by the presence of constitutional symptoms, vital organ compromise, bone marrow involvement, rapid progression and transformation as defined by the Groupe d'Etude des Lymphomes Folliculaires (GELF), BNLI or National Comprehensive Cancer Network (NCCN) criteria [10,11,101]. On the other hand, starting treatment at diagnosis may overcome tumor resistance by treating the disease when it is more susceptible, and consequently might improve duration of response or progression-free survival (PFS) [6–9]. In several randomized controlled trials (RCTs), combined rituximab plus chemotherapy (R-chemotherapy) demonstrated improvements in overall response rate (ORR), response duration and PFS for untreated advanced-stage FL patients, and has shown overall survival (OS) benefits in some of these trials when compared with chemotherapy alone (Table 1) [12–15]. While randomized data provide evidence that chemotherapy regimens given with rituximab provide benefits over the same chemotherapy regimen given alone, there is little published data from randomized controlled clinical trials that compare R-chemotherapy regimens to each other. Therefore, the addition of rituximab to chemotherapy has become ubiquitous, but debate remains regarding which patients are best suited for each R-chemotherapy combination [16–19].

Attempts to extend the duration of remission following induction therapy have been undertaken. Data from the PRIMA study, in which patients who responded to R-chemotherapy were then randomized to rituximab maintenance or observation, demonstrated that those who received maintenance therapy had a significantly prolonged PFS [20]. For patients who did not receive rituximab with induction chemotherapy, reports from the FIT trial demonstrated consolidation with radioimmunotherapy (RIT) could also extend PFS in comparison to those who were observed, and has potential to deepen the response to induction therapy [21]. Treatment with RIT has been recommended for patients with relapsed or refractory FL, and may be a useful therapy for primary refractory disease [22]. Emerging evidence has shown that consolidation treatment with RIT is an innovative treatment strategy to increase complete response (CR), thereby prolonging PFS. An international, randomized, Phase III trial of ⁹⁰Y-ibritumomab tiuxetan, the FIT trial [21], demonstrated the efficacy and safety of consolidation with RIT in patients with advanced-stage FL. Among 414 patients (consolidation, n = 208; control, n = 206), ⁹⁰Y-ibritumomab tiuxetan consolidation significantly prolonged median PFS (36.5 vs 13.3 months in the control arm, hazard ratio = 0.465; p < 0.0001), and remarkably, converted 77% of patients in

partial response (PR) to CR/unconfirmed CR, achieving a final CR rate of 87%. The study led to its approval by EMA as consolidation therapy following remission induction in previously untreated patients with FL. Consistent with these results, the FLUMIZ trial of consolidation with ^{90}Y -ibritumomab tiuxetan in previously untreated patients had achieved 96.5% of CR, 76% of OS and 100% of PFS [23].

WW as an initial management strategy

Although WW remains a reasonable initial strategy for FL because RCTs demonstrated no clear benefit when comparing older chemotherapy agents to WW [10,11,24], it is not clear whether WW is still a useful strategy when compared with modern therapies for FL.

The early rationale for WW was based on a Stanford study that examined whether immediate initial treatment is necessary in asymptomatic patients with stage III or IV NHL [25]. Based on study defined criteria, 44 patients were followed from 3 to 133 months without any initial treatment from 1963 to 1978. At the time of follow-up, treatment had been given to 25 patients with a median time to therapy of 31 months. Treatments given to these patients included single-alkylating-agent chemotherapy (13 patients), combination chemotherapy (6), local-field radiation therapy (4) and whole-body irradiation (2). Median actuarial survival for all 44 patients was 121 months. These results suggested that patients with advanced-stage low-grade NHL could have a good prognosis without any initial therapy.

A follow-up study analyzed 83 patients in total with advanced-stage NHL of low histologic grade followed without initial therapy [26]. Treatments were initiated at disease progression, and included radiation and chemotherapy. Patients were followed for 11 months to 17 years, with a median follow-up period of 50 months. For results comparison, another 131 patients who received immediate treatment on clinical protocols were examined. The OS rates for the group were 82 and 73% at 5 and 10 years, respectively. The median OS was 11 years. The 5-year OS for the protocol patients was 77%. The transformation incidence, median time to transformation and transformation risk at 8 years in this study were 12%, 57 months, and 19%, respectively, compared with 18%, 54 months and 23% for the protocol-treated patients. These results indicated that the transformation risk did not appear to be influenced by the choice of immediate or deferred treatment. In summary, this study showed that deferring treatment until there was progressive disease (PD) did not compromise survival, and could also be beneficial for asymptomatic patients by avoiding the adverse effects of cytotoxic therapy.

Randomized trials comparing WW & chemotherapy

Following these early observational studies, RCTs were performed to compare WW to initial chemotherapy. In a RCT, Ardeshtna and colleagues compared administration of immediate chlorambucil treatment with a policy of delaying chlorambucil until clinical progression necessitated its use, in asymptomatic patients with advanced-stage, low-grade NHL [10]. both groups, local radiotherapy (RT) to symptomatic nodes was allowed. Median follow-up was 16 years. OS and cause-specific survival did not differ between the two groups (median OS: oral chlorambucil 5.9 [range 0–17.8] years vs observation 6.7 [0.5–18.9] years, $p = 0.84$; median cause-specific survival 9 [0–17.8] years and 9.1 [0.67–18.9] years, respectively, $p = 0.44$). The actuarial probability of not needing chemotherapy (nonlymphoma deaths censored) at 10 years was 19% overall. In the WW group, 73% of patients received treatment with a median time to first treatment of 2.6 years. Patients <70 years and male patients tended to be more likely to need chemotherapy eventually.

In a second randomized study, Brice and colleagues prospectively evaluated three interventions for patients with FL and low tumor burden: delay of any treatment until clinically meaningful progression, immediate treatment with an oral alkylating agent, or treatment with a biologic response modifier, IFN α -2b [11]. With a median follow-up of 45 months after randomization, the median freedom from treatment (FFT) interval was 24 months for individuals undergoing WW and the freedom from treatment failure (FFTF) was 40 and 35 months for prednimustine and interferon, respectively. The median OS time was not reached for any arm. At the median follow-up time, high tumor burden was present in 67% (arm 1), 51% (arm 2) and 58% (arm 3) of patients. The OS at 5 years was 78% in the observation arm, 70% in patients receiving prednimustine and 84% in patients treated with interferon. No significant prognostic factor was found for survival. The authors concluded that deferring treatment did not adversely influence survival and was feasible in patients with FL and a low tumor burden. Furthermore, the authors proposed that deferring the treatment could lower the long-term toxicity induced by treatment.

Another prospective trial examined radically divergent treatment approaches [24]: 44 were randomly assigned to WW, in which only limited RT was administered, if necessary, and 45 were randomly assigned to ProMACE-MOPP (aggressive combined modality treatment with prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine and procarbazine), followed by total nodal irradiation. Of 41 evaluable patients receiving WW, 23 (56%) had not required systemic therapy at the time of publication, although 16 (39%) had received RT. The median time to crossover was 34 months. While this study showed a favorable 4-year disease-free survival of 51% with ProMACE-MOPP compared with WW (12%) [24], an updated report with median follow-up of 13 years found no differences in OS [27]. A total of 75% of patients following ProMACE-MOPP were alive and free of cancer, while 75% of WW patients were alive with lymphoma. A recent study [28] has addressed the relative benefits of first-line R-CHOP-14 (rituximab, cyclophosphamide, hydroxydaunomycin [doxorubicin], oncovin [vincristine] and prednisone) versus R-CHOP-21 in the optimizing treatment of indolent B-cell lymphoma with rituximab. The randomized trial revealed remarkably comparable complete remission rate, PFS and OS, with more grade 4 neutropenia and grade 3 infection observed in the R-CHOP-21 group; thus, the R-CHOP dose-dense strategy failed to indicate any benefit. Furthermore, a recent randomized study comparing R-CVP (rituximab, cyclophosphamide, vincristine and prednisone), R-CHOP and R-FM (rituximab, fludarabine and mitoxantrone) has shed light on the debate about the potential benefit among the regimens of rituximab with chemotherapy [16]. The 3-year OS was comparable; however, R-CVP was associated with inferior 3-year time-to-treatment failure and PFS compared with the other regimens, and R-FM displayed a higher rate of secondary tumors. Thus, short- and long-term toxicities, patient median survival, as well as patient age and comorbidities, should be incorporated into the decision making regarding treatment for individual patients and in designing comparative studies.

Rituximab single-agent therapy

FL has the immunophenotype of being CD19-, CD20- and CD22-positive, and CD5-negative. Rituximab, a chimeric anti-CD20 immunoglobulin, was the first commercially available monoclonal antibody for the treatment of lymphoma, with suspected mechanisms of action being complement-mediated lysis, antibody-dependent, cell-mediated cytotoxicity, and binding of the CD20 cell surface antigen and induction of apoptosis [29,30]. Other than infusion-related toxicities, which are often self-limited, rituximab is generally well-tolerated and treatment can be repeated without substantial cumulative toxicity. Because of these characteristics, rituximab has been raised as an alternative option to observation for patients diagnosed with asymptomatic, advanced-stage FL.

In one study, Witzig and colleagues administered rituximab 375 mg/m² intravenous weekly for four doses to 36 patients with newly diagnosed, untreated FL grade 1, and measurable, stage III/IV disease [31]. The ORR was 72%, with a CR rate of 36%. Two patients died without PD, and three died with PD. The median time to progression was 2.2 years. Eighteen patients were subsequently treated with chemotherapy, with a median time to chemotherapy of 2.3 years. Patients with high lactate dehydrogenase (LDH) levels had a lower ORR of 33% and a short time to progression of only 6 months. These data suggest that rituximab can be safely administered to patients with advanced-stage FL grade 1 with efficacy and minimal toxicity, and offers an acceptable alternative to WW in this patient population. However, single-agent rituximab does not appear to be an effective treatment option for patients with elevated LDH.

Comparisons of initial treatment with rituximab & WW

An unpublished RCT designed to compare a WW approach with immediate treatment with rituximab enrolled patients with asymptomatic stage II FL and adequate bone marrow reserve who were randomly assigned with a ratio 1:1:1 to WW or rituximab 375 mg/m² weekly for 4 weeks (later dropped from the trial) or rituximab 375 mg/m² weekly for 4 weeks followed by rituximab maintenance every 2 months for 2 years (starting at month 3). The primary end points were time to initiation of new therapy (chemotherapy or radiotherapy) and effect on quality of life. A total of 95% of patients had low tumor burden by GELF criteria; the FL international prognostic index (FLIPI) scores were: 0 = 9%, 1 = 26%, 2 = 41%, 3 = 22% and 4 = 2%. An interim analysis was performed and, at month 7, spontaneous remission was seen in 3%, PR in 6%, stable disease in 74%, and PD in 17% of WW and for rituximab followed by maintenance there was a CR/unconfirmed CR rate of 49%, PR of 36%, stable disease in 11%, and PD in 3%. The PFS and time to initiation of new therapy were significantly longer in the rituximab groups. The authors concluded that these data indicated that initial treatment with rituximab significantly delays the need for new therapy, and that this finding may change the management of patients with newly diagnosed asymptomatic FL [32]. Data from the NLCS, a prospective, multicenter, observational study collecting data on FL patients diagnosed from 2004–2007 at 265 US sites (80% nonacademic) also showed statistically significant differences in PFS and time to chemotherapy comparing rituximab and WW [33]. However, controversy remains regarding whether PFS is a meaningful end point for comparing an active therapy to WW, and it remains to be seen how these results will impact the management of patients with asymptomatic low tumor burden FL.

A randomized Phase III study investigated two strategies of rituximab treatment in patients with advanced-stage FL and low tumor burden [34]. This patient population is one in which WW may have been an appropriate management strategy, but as described above, clinicians may also choose an initial management of single-agent rituximab. This study examined whether there was a longer duration of benefit from rituximab with continued maintenance in responders to induction rituximab versus retreatment with rituximab at progression. The preliminary findings from this study reported no difference in time to treatment failure between the two approaches. Interestingly, at 3 years, 95% of patients in the rituximab maintenance arm and 86% in the retreatment arm remained free of cytotoxic therapy, an improvement over historical controls with WW.

Given the availability of well-tolerated therapy such as immunotherapy, it is not surprising that utilizing these agents in asymptomatic patients is an attractive strategy and one that challenges the historical end points for WW. With development of additional therapies that hold promise to be well tolerated, this debate may continue. Targeting the B-cell receptor signaling pathway with agents such as the BTK inhibitor PCI-32765 and CAL-101

(GS-1101), a small-molecule inhibitor that selectively targets PI3K δ , are promising approaches that have demonstrated single-agent activity in relapsed patients and are well tolerated [35,36]. Newer generations of monoclonal antibodies are also being investigated in clinical trials, with promising agents such as ofatumumab with high overall response rates [37]. Lenalidomide has also demonstrated activity as a single agent and is even more effective when combined with rituximab based on Phase II results [38]. All of these agents hold promise given their activity and tolerability, raising more questions as to the timing and sequencing of therapy for patients with FL.

Mathematical modeling to support FL clinical decision-making

Given new data regarding the initial management strategy for asymptomatic patients with advanced-stage (III/IV) FL, emerging new strategies for FL, and the variable clinical course of FL, clinical decision-making is becoming increasingly challenging. While GELF, NCCN and BNLI criteria may aid clinicians in determining when to treat, these criteria provide minimal guidance in selecting what treatment to administer. Moreover, these measures provide criteria for when it becomes dangerous to continue observation, not when it is optimal to begin treatment to maximize effectiveness. In this context, efficient risk estimation tools would be helpful to stratify patients and tailor treatment strategies for different patient subgroups.

FLIPI [39] and its variant FLIPI2 [40] are currently the most commonly used prognostic tools for FL patients. FLIPI2 was developed in a prospective study using PFS as a surrogate for OS. While the FLIPI2 provides a useful prognostic model for FL, this index utilizes a laboratory value that may not be routinely collected in clinical practice – β -2 microglobulin. Although it has been shown that patients stratified in expected PFS and OS by FLIPI, and PFS by FLIPI2, these indices still suffer from several limitations for use as clinical decision support tools. First, the risk estimations by the FLIPI were not designed to be treatment specific. That is, the effects of treatment cannot be considered by the FLIPI, because the FLIPI index was derived from a retrospective study of a general population of patients receiving different types of treatments. However, emerging data suggest that FLIPI can predict outcomes across a number of commonly used treatments [41]. Second, the FLIPI does not provide enough information for clinical decision-making. Estimates for PFS and response rates are not yet broadly available or utilized in a treatment-specific fashion by FLIPI. Moreover, categories of some risk factors in the FLIPI may need to be refined. For example, patients between the ages of 60 and 90 years are in the same age category defined by the FLIPI, but they may need different treatment strategies. Lastly, the FLIPI cannot provide sufficient treatment-specific risk estimates to guide the initial management for the subgroup of patients with low-tumor burden, and to help determine which patients should undergo WW and which patients might benefit from more immediate treatment. Despite these limitations, FLIPI remains a useful prognostic index in patients treated in community practices according to an analysis of the NLCS [41]. Stratifying patients into FLIPI risk groups generally predicts outcomes in terms of PFS, OS and time to next treatment. FLIPI2 holds promise to provide accurate prognostic information in the immunotherapy era, and may be widely accepted once validated. FLIPI and FLIPI2 are promising tools for stratifying patients in clinical trials and might be adapted to aid in comparative effectiveness research [42]. However, use of both has been hampered by the need for laboratory testing (LDH and β -2 microglobulin) at diagnosis, which, when unavailable, limit the ability to define a complete prognostic score. Improving clinicians' awareness of these tests and the benefits of providing prognostic information to patients may enhance utilization of these tools in the future. Similarly, fluorodeoxyglucose-PET has been proposed as a means for stratifying patients and defining treatment strategies for patients with FL. However, many limitations exist for use of this technology for FL that are beyond the scope of this article. Current

International Working Group Guidelines do not recommend routine use of fluorodeoxyglucose-PET to guide treatment decision-making for FL.

To support clinical decision-making, modeling the clinical course of FL can be a very important supplement to RCTs and observational studies. Although RCTs are the conventional methods to guide clinical decision-making, because RCTs are designed to test a specific hypothesis, they often provide insufficient data for answering real-world clinical questions. Optimizing treatment is sufficiently complex that RCTs cannot address all pertinent scenarios. Furthermore, RCTs are not always feasible because, in some cases, there are numerous alternatives that need to be tested against each other, RCTs take a very long time to develop and to provide data, and they are often very costly. This is particularly true in the case of providing guidance for the management of FL, where there are many possible treatment sequences with different durations, which are almost impossible to test against each other in a typical RCT, and patients' outcomes after treatments depend on multiple clinical features interacting with each other, which would be very difficult to capture in an RCT. Finally, as the studies above illustrate, most patients with FL live for such a long time with modern treatments, regardless of the intervention, that measuring treatment benefits using OS will no longer be practical.

Mathematical modeling is a novel alternative approach to RCTs and observational studies that can be used to guide clinical decision-making. Mathematical models build a logical framework to synthesize information from various sources that are otherwise difficult to consider simultaneously [42]. Mathematical models may be useful for discovering the intuition and insights for optimal clinical decisions. Examples of mathematical models that might be useful in clinical decision-making include computer simulation models, decision trees, neural networks, statistical models (e.g., regression models), Markov models and Markov decision processes. Several mathematical models have been developed and have been successfully applied in many other cancers including breast [43,44], colorectal [45] and cervical cancer [46], as well as other diseases including end-stage liver diseases [47,48], heart diseases [49] and HIV [50]. Furthermore, several models have been useful to provide evidence for many health policy problems. For example, the recent mammography screening guidelines by the US Preventive Services Task Force (USPSTF) were based on the findings of several natural history simulation models of breast cancer epidemiology developed by the Cancer Intervention and Surveillance Modeling Network (CISNET) researchers [15,51].

The management of FL is so complicated that clinical decisions require consideration of many factors simultaneously, including patients' demographic and clinical features, as well as treatment efficacies, where many clinical questions can be addressed by mathematical modeling in a systematic and comprehensive way. For example, what is the impact of WW to the subsequent treatment effectiveness? What is the optimal time to start treatment? What are the optimal treatment sequences for an individual patient? Addressing such questions via RCTs and observational studies would be extremely difficult, if not impossible. To answer such questions, we propose a computer simulation model that can replicate the natural history of FL progression, as well as the surveillance and treatment outcomes in the population. Much work in parameter estimation and model calibration needs to be carried out carefully. A well-developed simulation model may provide outcome estimates of the clinical course (such as PFS, OS, transformation risk and so on) based on patients' clinical features and different treatment strategy settings. These outputs may be informative for guiding clinical decisions. An illustrative diagram of such a modeling framework is presented in Figure 2.

A novel modeling approach, adaptive treatment strategy (ATS), has been introduced for management of diseases that require sequential treatments during a relatively long disease

course [52,53]. Instead of a fixed (optimal) sequence of treatments, the ATS approach can be an alternative way to define optimal treatment strategies [53]. An ATS is implemented according to a decision rule, in which treatment decisions (i.e., dose, duration, type and so on) are tailored based on individual factors such as patient risk factors, responses to preceding treatments and individual adherence rate [54–57]. One example of this approach is the construction of ATS for patients with depressive disorder from data collected from a sequential, multiple assignment, randomized trial (SMART) [58,59]. The ATS takes advantage of the diagnostic effect of a treatment, which means that the response results of a treatment could be informative for physicians to determine the optimal next line of treatment. However, it is often easily overlooked [54]. An ATS model may adequately support treatment planning for patients with FL, since such models can simulate the long clinical course of the disease with varying treatment options at each relapse, and provide data on the optimal timing and sequence of therapies. With the goal of maintaining a long lifetime and a good quality of life, the decisions in subsequent treatments (i.e., when and what) will depend on the patient response as well as side effects of preceding treatment. Future research may try to overcome the difficulties in constructing ATS models with limited data for the management of FL.

Conclusion & future perspective

Although well-formulated management strategies for FL exist [6–9,60], applying these guidelines to make individual treatment decisions for patients with FL remains challenging. Risk-adapted treatment strategies for FL are needed.

At present, a WW strategy is generally recommended for asymptomatic low tumor burden FL patients with advanced-stage disease, since early systemic treatment has not demonstrated benefits in OS compared with WW, and the PFS and time to next treatment benefits of such approaches remain debatable. However, first-line rituximab monotherapy has demonstrated very high response rates of 70–80%, and can produce long PFS [31,61,62]. Moreover, the addition of rituximab to several chemotherapy regimens (CHOP, CVP, MCP and FCM) improved the response rates, PFS and, in certain cases, OS compared with the conventional chemotherapy alone [17,18], but limited data are available to aid in selecting among chemotherapy regimens for a particular patient. While the FLIPI is useful in stratifying patients for comparing results of clinical studies, most clinical trials do not compare the outcomes of treatments between patient subgroups stratified by the FLIPI. Moreover, FLIPI has not been used to predict the need for treatment, or the responsiveness to a specific treatment. Validated biomarkers are desperately needed to help individualize treatment strategies. In addition, risk estimation models and mathematical models may be helpful in a more systematic risk analysis and effectiveness comparison between alternative treatment strategies under various assumptions. These clinical data-driven mathematical models may have the potential to aid in first-line treatment selection for patients with FL and improve clinical decision-making.

Acknowledgments

This work was supported by CR Flowers' American Society of Hematology Amos Medical Faculty Development Award, a Georgia Cancer Coalition Distinguished Scientist Award and Cancer Research Award and R21 CA158686-01A1. CR Flowers has also received research funding from Abbott, Celgene, Millennium/Takeda, Spectrum, Janssen Pharmaceutical, Calistoga Pharmaceuticals, Eastern Cooperative Oncology Group, Southwest Oncology Group, National Cancer Institute, NIH, Northwestern University and Memorial Sloan Kettering Cancer Center. CR Flowers is a consultant for Genentech/Roche, Millennium/Takeda, Celgene, Seattle Genetics, Prescription Solutions, Clinical Care Options, Spectrum, American Society of Hematology and American Society of Clinical Oncology. LJ Nastoupil is a consultant for Genentech/Roche and R Sinha has received research funding from Celgene.

No writing assistance was utilized in the production of this manuscript.

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■ ■ of considerable interest

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Box 1**the Groupe d'Etude des Lymphomes Folliculaires and British National Lymphoma Investigation criteria for initiation of therapy****GELF criteria[†]**

- Involvement of >3 nodal sites, each with a diameter of >3 cm
- Any nodal or extranodal tumor mass with a diameter of 7 cm
- Presence of type B symptoms
- Risk of local compressive symptoms that may result in organ compromise
- 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)
- Splenomegaly (>16 cm on CT scan)
- Pleural effusion or peritoneal ascites

BNLI criteria[‡]

- Rapid generalized disease progression in the preceding 3 months
- Presence of type B symptoms or pruritus
- Life-endangering organ involvement
- Bone marrow compromise (leukocytes $<1.0 \times 10^9/l$, hemoglobin <10 g/dl or platelets $<100 \times 10^9/l$)
- Renal infiltration
- Bone lesions
- Macroscopic liver involvement

[†]Data taken from [11].

[‡]Data taken from [10].

BNLI: British National Lymphoma Investigation; GELF: Groupe d'Etude des Lymphomes Folliculaires.

Practice Points

- Clinicians should be aware of the marked heterogeneity in the initial presentation of follicular lymphoma (FL) and the patterns of disease relapse.
- Patients should be evaluated using the the FL international prognostic index (FLIPI) and FL international prognostic index 2 (FLIPI2) and informed about the expected prognosis based on these indices.
- Patients should be evaluated using the criteria defined by the Groupe d'Etude des Lymphomes Folliculaires (GELF) or other criteria to determine the tumor burden at diagnosis, and this should be used to tailor discussion regarding the need for therapy and type of therapy.
- Clinicians should be aware of relevant data regarding single-agent rituximab and watchful waiting for low tumor burden patients, and discuss these findings with patients in making treatment decisions.
- Combination regimens with rituximab and chemotherapy (chemoimmunotherapy) have demonstrated benefits over chemotherapy alone.
- Clinicians should evaluate recent data comparing various chemoimmunotherapy regimens and use these data in decision-making regarding the most appropriate choice for individuals with advanced stage FL.

Figure 1. Management strategies for follicular lymphoma

†Bulky, abdominal disease.

‡According to the Groupe d'Etude des Lymphomes Folliculaires criteria.

RIT: Radioimmunotherapy; RT: Radiotherapy.

Figure 2. A framework for a mathematical simulation model of the clinical course of follicular lymphomas

CR: Complete response; PR: Partial response; SD: Stable disease.

Table 1

Adding rituximab to front-line chemotherapy improves response rates, progression-free and overall survival.

Regimen	n	CR (%)			PFS (%)		OS (%)		Ref.
		R-chemo	Chemo	End point (years)	R-chemo	Chemo	R-chemo	Chemo	
R-CHOP	428	44	35	2	82 [†]	64	95 [†]	90	[13]
R-CHVP-IFN	358	63	34	5	52 [†]	37	84	79	[15]
R-CVP	201	50 [†]	25	4	71 [†]	40	87 [†]	74	[14]
R-MCP	201	50 [†]	25	4	71 [†]	40	87 [†]	74	[12]

[†] Statistically significant improvement for rituximab with chemotherapy compared with chemotherapy among patients who required therapy.

Chemo: Chemotherapy; CR: Complete response; OS: Overall survival; PFS: Progression-free survival; R-chemo: Combined rituximab plus chemotherapy.