Aiming at a Curative Strategy for Follicular Lymphoma

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ABSTRACT  Follicular lymphoma is often managed as an incurable disease. However, a substantial and growing fraction of patients are achieving long-term disease-free survival from aggressive treatment approaches. The application of novel therapeutic tools, including monoclonal antibodies, radioimmunootherapy, and vaccines, as well as new and more active chemotherapeutic agents, is producing complete responses in the majority of treated patients, with a 2-fold increase in disease- and progression-free survival in randomized trials. For some of these treatment approaches, follow up has not yet been long enough to determine a median response duration, but it certainly exceeds the “2 to 3 years” that is routinely stated as dogma to patients with this illness. Furthermore, some patients remain in complete remission beyond a decade from their initial treatment, implying that the assumption of inevitable relapse also must be challenged. One clear fact is that no patients will ever be cured by adopting a palliative treatment approach. The assumption that patients with follicular lymphoma are incurable is certain to be a self-fulfilling prophecy. Here the author summarizes the large and growing body of knowledge that suggests an expectant approach to management is not appropriate for all patients. (CA Cancer J Clin 2008;58:305–317.) © American Cancer Society, Inc., 2008.

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GENERAL OVERVIEW

Follicular lymphoma (FL) was first described in 1925 as a benign disorder called Brill–Symmers disease, but within a couple of decades, it was recognized as a malignancy typical of adults and the elderly, whose clinical course is mostly indolent and unpredictable. It currently arises at a frequency of roughly 1 new case every 20,000 to 25,000 people per year in the Western world. After several decades of limited progress in FL clinical research, due in part to low rates of enrollment in clinical trials, in recent years a growing number of reports have finally led to an acceptance of the notion that survival of FL patients is improving. Therefore, historical dogmas concerning the natural course of the disease and the way we try to change it must be challenged. Examples of these dogmas are that patients should not be treated until they become symptomatic; that FL is incurable and, as such, it is always acceptable to treat it with palliative intent; that aggressive therapies should be postponed as long as possible; that transformation of FL into a more aggressive lymphoma is a natural feature of the disease independent of previous treatments; and that median overall survival (OS) of FL patients is about 8 to 10 years. Indeed, the improvement in survival appears to depend mostly on the progressive shift from a watchful-waiting or a palliative initial approach to novel, combined-modality strategies that are either more intensive or better tailored to patients according to clinical prognostic factors. Even more progress may be possible if the choice among therapeutic options becomes directed by the application of a number of biologic prognostic factors identified over the last decade.

One feature of FL that has certainly not yet changed is its extreme clinical variability, which most likely reflects the complex and incompletely understood physiopathology of the disease. Consequently, and in contrast to most other malignancies, a continuous complete response (CR) longer than 10 years is per se unacceptable as a conceptual surrogate to define cure in FL. Therefore, both newly diagnosed and long-term indolent FL patients are technically precluded from being considered curable by the very fact that, paradoxically, no suitable definition of cure

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exists for them. Indeed, no incurable disease can become curable unless a manageable definition of cure is established for it and agreed on. One proposal for a definition of FL cure has been a remission that continues indefinitely, with the patient eventually dying of another disease.\textsuperscript{11} Certainly, most patients who fulfill such criteria might be considered cured; however, no long-term follow-up studies of patients dying from other causes while in remission have confirmed the absence of disease by pathologic criteria. Should one consider such a patient cured if microscopic bone marrow involvement with lymphoma were documented? Indeed, many of the therapies currently in use may be maintaining disease at a subclinical tumor burden rather than eradicating it. Does the presence of subclinical levels of tumor influence the duration or quality of life? This answer is not yet fully known. A definition of cure that depends on obtaining decades of patient follow up is unlikely to become a reasonable basis for a clinical trial endpoint. Still, at the same time, clinical trials of potentially curative treatments must be conducted and cure must be pursued because most FL patients prefer to individually search for the elusive cure rather than accepting enrollment in clinical trials that do not even consider achieving it. Moreover, it has to be considered that not all patients need to be cured of their FL, particularly those who, due to age and/or tumor indolence, may have a life expectancy and a quality of life not inferior to those of their healthy counterparts.

**BIOLOGIC FEATURES**

The first molecular step toward development of FL is the acquisition of t(14;18) by pre-B cells during an abnormal immunoglobulin rearrangement in the bone marrow. In healthy individuals, t(14;18)-positive cells are of no importance unless they meet an antigen and are driven into a T-cell–dependent reaction within the lymph node germinal center.\textsuperscript{12} In this context such cells acquire a proliferative and/or survival advantage over their normal counterparts and, through an accumulation of genetic alterations,\textsuperscript{12} are converted into the bona fide FL clone, which ultimately loses its growth dependence on the antigen.\textsuperscript{12,13} The most notable consequence of t(14;18) is overexpression of \textit{bcl2} protein. The ability of \textit{bcl2} to protect the cell from apoptosis may be the basis for the growth advantage of t(14;18)-positive cells.\textsuperscript{12} It is still not completely established whether the t(14;18)-positive cells frequently detected in healthy individuals\textsuperscript{14} increase the risk of subsequently developing FL. FL patients are more frequently positive and consistently show higher numbers of such cells than healthy individuals.\textsuperscript{15} Meanwhile, healthy individuals and patients with malignancies other than lymphoma present similar numbers at diagnosis, but t(14;18)-positive cell frequency significantly drops after chemotherapy in the latter group.\textsuperscript{16}

Incomplete understanding of pathogenesis and methodological uncertainty clearly explain why even today it is impossible to determine whether eradicating the t(14;18)-bearing clone (ie, achieving molecular remissions) is an important goal of therapy. Over the last decade, a number of reports have reached contradictory conclusions on this subject. Some studies have shown a clear-cut correlation between post-treatment \textit{bcl2}/IgH rearrangement status and remission duration,\textsuperscript{17,18} while others have not, including those with longer follow up\textsuperscript{19} and those analyzing not just the major but also most minor breakpoints\textsuperscript{20,21} and even the subset of follicular large–cell lymphoma.\textsuperscript{22}

Finally, some FL cases do not feature the \textit{bcl2}/IgH rearrangement at all, or contain the translocation but do not express the resulting gene product, or give rise to false-negative results due to \textit{bcl2} gene mutations.\textsuperscript{23,24} This group comprises up to 30% of FL in some series.\textsuperscript{25} However, a consistent picture of the effect of the absence of the translocation or the \textit{bcl2} protein has not emerged.\textsuperscript{26}

Known for its generally indolent behavior, FL may undergo more aggressive histological and clinical transformation at a rate of about 3% per year.\textsuperscript{27} To further complicate the understanding of this process, transformed FL presents as a germinal center–like malignancy that may evolve by at least 2 pathways: one that is similar in proliferation rate to the previous FL and whose oncogenic routes are largely undefined and the other with both higher proliferation rate and recognized oncogenic abnormalities.\textsuperscript{28}
HISTOLOGIC FEATURES

After considerable debate surrounding the reproducibility of the methodology and its clinical validity, the authors of the World Health Organization (WHO) Classification of Lymphoid Malignancies ultimately decided to retain the original division of FL into 3 histologic grades. FLs generally are a mixture of clonally related small B cells with cleaved nuclei and large B cells similar to those of diffuse large B-cell lymphoma. FL is divided into 3 grades based on the frequency of the large cells. Formerly, these grades were given different names: follicular, small-cleaved cell; follicular mixed; and follicular large-cell lymphoma. According to the “Berard criteria” (Table 1) currently used by most pathologists to grade FL, Grade 1 consists predominantly of small cells (centrocytes), Grade 2 consists of a mixture of both small and large cells (centroblasts), and Grade 3 features a predominance of large cells. As a result of renewed concerns about the reproducibility and clinical relevance of this grading, the imminent revision of the WHO non-Hodgkin lymphoma (NHL) classification is expected not to include the Berard criteria for grading FL, but rather to consider FL as a single histologic entity (FL), solely to be kept separated from former Grade 3b (centroblastic FL or FL/large cell) (Table 1). However, this residual discrimination is due more to uncertainty about possible biologic and clinical differences than to well-defined data documenting the ultimate impact of such variables. Finally, the new WHO NHL classification is also expected to recognize cutaneous FL as a new entity, other extranodal FL as different varieties, and pediatric FL as a novel subtype (S. Pileri, MD, oral communication, May 7, 2008).

While the use of histologic grading is expected to decline, a number of reports have suggested the prognostic importance of some tissue architectural details. Among others, 2 prospective studies have shown how FL patient survival can be predicted by accurate analysis of peculiar features of either bone marrow or lymph node specimens. The former has established in multivariate analysis the adverse influence of a high number of lymphomatous foci within the initial bone marrow biopsy on event-free survival and of the presence of 2 different histologic patterns (ie, nodular and diffuse) on event-free survival and OS. The latter indicated poor FL OS was solely associated with the presence of tumor sclerosis within the diagnostic lymph node.

Over the last 3 to 4 years, a conspicuous number of retrospective reports based on both gene-expression profiling and immunohistochemistry conducted on initial FL diagnostic specimens have suggested that FL is a disease characterized by functional interactions between tumor cells and their local microenvironment and that the functional composition of the microenvironment influences the clinical behavior. The general concordance of all studies would seem to allow the potential classification of most, if not all, FL cases into 2 subgroups: those in which the reactive microenvironment features an immune-surveillance pattern (typical T cells and STAT1-negative macrophages) associated with better outcome and those in which it features an immune-escape pattern (CD57-positive lymphocytes) associated with worse outcome. Unfortunately, data are not available on FL lymph nodes undergoing spontaneous regression to see whether these histologic features are also present in a setting where the tumor is shrinking. Moreover, as it happens with most histologic prognostic factors in FL, a role for tumor-infiltrating macrophages and T cells in predicting outcome has not been confirmed by others who have examined the question. In one of the prospective studies mentioned previously, no prognostic correlation was found with macrophage or T-cell count in the tumor microenvironment, nor with grading and proliferation index.

### TABLE 1 Berard Criteria for Follicular Lymphoma Grading

| Grade | Definition |
|-------|------------|
| 1     | 0 to 5 centroblasts/HPF |
| 2     | 6 to 15 centroblasts/HPF |
| 3     | >15 centroblasts/HPF |
| 3a    | >15 centroblasts but centrocytes are still present |
| 3b    | Centroblasts form solid sheets with no residual centrocytes |

Abbreviation: HPF, high-power field.
Most FL cases are diagnosed by histologic examination of a persistently enlarged lymph node harvested from an otherwise asymptomatic patient. Before treatment, diagnosis should be confirmed by an experienced hematopathologist with expertise in lymphoma. Fine-needle aspiration should not be considered appropriate for initial diagnosis. On diagnosis confirmation, patients must undergo staging in order to establish whether they have limited (Stage I to II) or advanced (Stage III to IV) disease (Table 2) because the 15% of patients with limited-stage disease often experience long-term continuous responses after local radiation treatment (RT) alone.

As mentioned previously, a minority of patients present with extranodal FL. In this case, symptoms are typically present that are not easily attributable to the lymphoma and are largely dependent on the actual location of the malignancy. Contrary to nodal FL, in this setting histologic diagnosis comes as a surprise in most cases.

Currently, at least 2 independent prognostic score systems are in use for FL: the Follicular Lymphoma International Prognostic Index (FLIPI), which is more widely used; and the Italian Lymphoma Intergroup (ILI) Index (Table 3). Both were defined retrospectively, before the introduction of rituximab therapy, and neither takes into account any of the putative biologic prognostic markers described previously in this review. However, the FLIPI appears to identify a larger proportion of high-risk patients than the ILI index, and it is useful in most clinical settings, including early-stage, first progression, histologic transformation, and autologous stem cell transplantation (SCT) and rituximab-treated FL patients.

### TABLE 2 Follicular Lymphoma Staging System

| Stage | Definition |
|-------|------------|
| I     | Single lymph node region (I) or one extralymphatic organ (IE) |
| II    | Two or more lymph node regions, same side of the diaphragm (II), or local extralymphatic extension plus lymph nodes, same side of the diaphragm (IIIE) |
| III   | Lymph node regions on both sides of the diaphragm, either alone (III) or with local extralymphatic extension (IIIE) |
| IV    | Diffuse involvement of one or more extralymphatic organs or sites |

| Variant | Definition |
|---------|------------|
| A       | No B symptoms |
| B       | At least one of the following: • unexplained weight loss >10% baseline during 6 months prior to staging • unexplained fever >38°C • night sweats |
| Bulky   | Any tumor diameter >10 cm |

### TABLE 3 Follicular Lymphoma Main Prognostic Indexes

**Follicular Lymphoma International Prognostic Index**: Low- (0 to 1 Adverse Factors), Intermediate- (2 Adverse Factors), High-risk (3 to 5 Adverse Factors) Patients

| Feature | Good Prognosis | Adverse Prognosis |
|---------|----------------|-------------------|
| Age     | <60 years      | >60 years         |
| Serum LDH level | Normal     | Above normal |
| Stage   | I to II        | III to IV         |
| Nodal sites involved | ≤4        | >4               |
| Hemoglobin level | ≥12 g/dl  | <12 g/dl         |

**Italian Lymphoma Intergroup Index**: Low- (0 to 1 Adverse Factors), Intermediate- (2 Adverse Factors), High-risk (≥ 3 Adverse Factors) Patients

| Feature | Good Prognosis | Adverse Prognosis |
|---------|----------------|-------------------|
| Age     | <60 years      | >60 years         |
| Serum LDH level | Normal     | Above normal |
| Sex     | Female         | Male              |
| Nodal sites involved | <2        | ≥2               |
| B symptoms | No        | Yes               |
| ESR     | <30            | ≥30               |

Abbreviations: LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate.
likely relevant during patient restaging and follow up should also be applied at diagnosis to facilitate accurate subsequent comparisons, even though at this time they may appear redundant or their actual importance is still unproven.58

Before treatment is started, newly diagnosed FL patients should undergo at least bone marrow biopsy, neck–chest–abdomen–pelvis computed tomographic scan, total body positron emission tomography,

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\text{\textsuperscript{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomographic scan}
\]

Nonmandatory but strongly recommended staging procedures

Pathology review by a hematopathologist with expertise in lymphoma

Optional staging procedures

Flow cytometry on the bone marrow aspirate

Molecular biology studies on the marrow aspirate

Selected nonroutine procedures depending on clinical presentation

Skin biopsy for suspected cutaneous localization

Otolaryngologic examination for suspected Waldeyer’s ring involvement

Gastrointestinal scopy with stomach and duodenum biopsies for suspected upper gastrointestinal tract involvement

Colonoscopy with colon biopsies for suspected colon involvement

TABLE 4  Initial Workup for Follicular Lymphoma

**Mandatory staging procedures**

- Complete history and physical examination with Eastern Cooperative Oncology Group performance score
- Complete blood count and differential
- Chemistry profile including creatinine, total protein, albumin, lactate dehydrogenase, and \(\beta-2\) microglobulin
- Erythrocyte sedimentation rate
- Bone marrow aspiration and biopsy (at least 2 cm core)
- Chest X-ray (posterior–anterior and lateral)
- Computed tomographic scan neck/chest/abdomen/pelvis

**Nonmandatory but strongly recommended staging procedures**

Pathology review by a hematopathologist with expertise in lymphoma

**Optional staging procedures**

Flow cytometry on the bone marrow aspirate

Molecular biology studies on the marrow aspirate

**Selected nonroutine procedures depending on clinical presentation**

Skin biopsy for suspected cutaneous localization

Otolaryngologic examination for suspected Waldeyer’s ring involvement

Gastrointestinal scopy with stomach and duodenum biopsies for suspected upper gastrointestinal tract involvement

Colonoscopy with colon biopsies for suspected colon involvement

Early-stage Disease

About 30% to 40% of Stage I and Stage II FL patients can be cured by involved field RT,73,74 with similar results being extrapolated also from studies on central lymphatic irradiation conducted before the advent of rituximab in Stage I to III FL.75 There is no comparative evidence that chemotherapy regimens can improve these results, although it remains possible that the addition of rituximab to chemotherapy might achieve this goal in the future. As for combined combination chemotherapy, together with the introduction of different immune-based maintenance approaches,63–65 has begun to change this somber situation.66 However, as mentioned previously, when cure becomes the goal, FL poses peculiar intellectual challenges because on one hand, some patients may experience long-term disease disappearance in the absence of any treatment, while others may endure long-term disease stabilization even without requiring therapy.66 As a consequence, particularly in the setting of newly diagnosed FL patients, the first challenge is distinguishing those most likely to benefit from an aggressive, curative-intent approach, which in certain cases might even include autologous or allogeneic SCT,67 from those who have nonlife-threatening disease.

Taking into account that the median life expectancy in Europe and North America is approximately 75 years for men and 80 years for women, at least in principle, tumor eradication should be the initial goal of treatment for most, if not all, FL patients under the age of 70 years. Above this age, it becomes arguable that competing causes may be more life-threatening than the underlying lymphoma, and the treatment for such patients may have effects on the quality of life that are unacceptable in some cases. For this reason, elderly patients, as well as patients with low-volume and/or very indolent advanced disease who are resolutely opposed to potentially more toxic treatment options that have as a goal long-term disease-free survival (DFS), can still be offered watchful waiting,68,69 single-agent rituximab,70 rituximab plus short-duration chemotherapy,71 low-dose RT,72 or a wide array of monochemotherapies such as chlorambucil.68
modality treatments, the few trials conducted so far have achieved rates of disease control and survival higher than those obtained by RT alone. However, these were single-arm studies, and as such they lacked any rigorously comparative intent.

**Advanced-stage Disease**

*The Impact of Rituximab*

Over the last decade, passive immunotherapy using the humanized anti-CD20 monoclonal antibody rituximab has changed the way we treat B-cell NHL. The mechanism of action of rituximab has not been fully elucidated yet, but antibody-dependent cellular cytotoxicity, complement-dependent cell cytotoxicity, growth inhibition, and inhibition of antiapoptotic prosurvival signaling pathways have been suggested.

The combination of rituximab with nearly any chemotherapy regimen is superior to the same chemotherapy regimen alone to the point that concomitant administration of rituximab and a chemotherapy regimen has rapidly become the first-line standard of treatment in FL. Currently, the sole ongoing trial challenging this novel paradigm without crossing the threshold between standard and high-dose chemotherapy is the SWOG S0016 study, which compares cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy plus rituximab with CHOP chemotherapy plus the anti-CD20 radioimmunotherapy agent tositumomab.

While longer follow up of all studies based on chemoimmunotherapy is warranted to ultimately assess whether the introduction of rituximab in first-line regimens results not just in improved relapse-free survival and progression-free survival (PFS) but even of OS, other randomized clinical trials have suggested that in either case, rituximab maintenance might achieve this long-sought goal at least in relapsed, recurrent, and resistant FL patients. Currently, the ongoing Phase III Primary Rituximab and Maintenance (PRIMA) study is trying to determine whether this result can be reproduced in newly diagnosed patients as well.

Finally, based on a single study suggesting that in patients with objective response or stable disease after treatment with single-agent rituximab, benefit is substantially but similarly prolonged by either scheduled maintenance treatment or rituximab retreatment at the time of progression, the ongoing Phase III Rituximab Extended Schedule or Retreatment (RESORT) study is being conducted to ascertain whether maintenance rituximab has more or less activity than waiting for clinical relapse to restart rituximab therapy.

**Primary Treatment Options**

Currently, an attempt to cure FL with first-line treatment may be, in theory, made through at least 2 different therapeutic strategies: combined chemoimmunotherapy and autologous SCT in first remission. Although chances of obtaining a long-term continuous first CR are higher with the latter option, the fact that a smaller percentage of patients treated with conventional-dose chemoimmunotherapy can achieve the same result with far less toxicity explains why the vast majority of FL patients do not receive autologous SCT as a consolidation of their first CR. Allogeneic SCT is also potentially curative, but its benefit is still powerfully offset by transplant-related mortality, while radioimmunotherapy is still far from having acquired a widespread acceptance as the first choice for newly diagnosed FL patients.

Which is the most effective combination chemotherapy regimen to use along with rituximab in previously untreated patients? The main contenders for primacy are CHOP and fludarabine-based regimens. CHOP is definitely the first choice worldwide among anthracycline-based regimens, while the variant excluding doxorubicin (CVP) tends to be reserved for elderly patients who require treatment, although no formal proof exists that CHOP is superior to CVP nor that use of the latter can be considered substandard. The CHOP regimen compares favorably with the combination of mitoxantrone, chlorambucil, and prednisone in terms of overall response rate (91% versus 82%; \( P < .026 \)) and does not compromise subsequent SCT feasibility because of prolonged myelosuppression (successful stem-cell collection rate: 93% versus 44%; \( P < .0003 \)). Fludarabine-containing regimens have emerged as a sound alternative, taking into account the following
points: the sole study prospectively comparing fludarabine, mitoxantrone, and prednisone with CHOP showed a higher response rate for the fludarabine combination (CR rate: 68% versus 42%; \( P < .003 \)), although the subsequent addition of rituximab to patients in both arms erased such differences, and similar survival rates were seen on both study arms.\(^{103}\) On the other hand, the later fludarabine-containing regimens are used in the treatment course, the more immuno-suppressive they are and the more likely to hinder pre-SCT mobilization they become, with an increased risk of severe infections.\(^{104}\) Moreover, fludarabine-containing regimens are poorly effective in cases of histologic transformation,\(^{104}\) as well as in follicular large-cell lymphoma.\(^{104}\) In these settings, anthracycline-containing combinations are superior.\(^{27,105,106}\) All in all, it is noteworthy that early first-line treatment has reported to reduce the incidence of histologic transformation compared with an expectant management approach (hazard ratio for expectant management 1.9; \( P < .008 \)).\(^{27}\)

**Salvage Treatment Options**

A number of salvage treatments may still have a chance to cure or at least conspicuously benefit a limited number of relapsed, recurrent, or resistant FL patients. They include chemioimmunotherapy regimens not used in first-line, rituximab alone, single-agent alkylators, or a variety of nonstandard options\(^{107}\) and are to be considered on a patient-by-patient basis not only for all FL cases who do not require a curative attempt, but also for those who may be at higher risk of complications if undergoing strategies based on high-dose chemotherapy. Yet, SCT remains central for most curative attempts in this situation. Since allogeneic SCT does not guarantee better results overall (OS at 5 years for allogeneic and autologous SCT: 51% and 55%, respectively),\(^{94}\) and it is not available for most patients, autologous SCT is most frequently used following high-dose chemotherapy conditioning. Total-body irradiation conditioning is rarely used in FL because of its late side effects, including myelodysplasia and second malignancies.\(^{108}\) Autologous SCT achieves results that can reverse the dogma stating that subsequent CRs tend to be shorter than previous CRs\(^{109}\) in patients with FL.\(^{110,111}\) Moreover, autologous SCT has also consistently shown a plateau in long-term FL survival curves,\(^{108,111}\) seems to succeed independent of the tumor grade,\(^{112}\) is not adversely affected by the introduction of rituximab in chemoimmunotherapy regimens used before transplantation,\(^{112,113}\) and compares favorably to alpha-interferon maintenance (PFS at 5 years: 65% versus 33%; \( P < .0001 \)).\(^{114}\)

Another novel and yet well-established therapeutic option for FL patients is radioimmunotherapy with the anti-CD20 monoclonal antibodies tositumomab, which is conjugated to 131-iodine, or ibritumomab tiuxetan, which is linked to 90-yttrium.\(^{95}\) While no trial has been conducted to prospectively compare the 2 agents, the growing literature concerning radioimmunotherapy has convincingly shown that single-agent, radio-conjugated monoclonal antibodies are more effective than single-agent rituximab in terms of CR (30% versus 16%; \( P < .04 \)) and overall response rates (80% versus 56%; \( P < .002 \))\(^{115}\) but are also more myelosuppressive,\(^{116}\) though they can be successfully used at lower dosages in patients prone to hematologic toxicity.\(^{117}\) They can also be combined with chemotherapy\(^{118,119}\) and used as first-line treatment.\(^{120,121}\) In this setting, a recent study has shown that consolidation with a single dose of ibritumomab tiuxetan following a fludarabine-based regimen improves PFS over observation (median PFS: 37% versus 13.5%; \( P < .0001 \)).\(^{122}\) However, it is also true that mainly due to logistical reasons, most FL patients are currently unlikely to receive either agent as part of a first-line treatment. Nevertheless, radioimmunotherapy has proved very effective also in previously treated FL patients,\(^{116,123–125}\) can be repeated,\(^{126}\) does not seem to increase the rate of treatment-related myelodysplastic syndromes and acute myeloid leukemia, though the median follow-up time and the numbers of subjects followed do not permit this complication to be accurately quantified,\(^{127}\) and has been claimed not to preclude the use of subsequent chemotherapy regimens in patients who may require them.\(^{128,129}\)

It is not yet clear whether radioimmunotherapy should be necessarily combined with autologous SCT when cure is the main goal of treatment, nor is it known whether radioimmunotherapy should be part of an SCT conditioning regimen.\(^{130,131}\)
or rather an earlier therapeutic step in the context of a sequential treatment culminating in an SCT conditioned by high-dose chemotherapy. What it is certain instead is that young, poor prognosis, relapsed, recurrent, or resistant FL patients deserve an early serious attempt at curative treatment. Most such patients do not have stem cells available at the time of relapse. Therefore, a short course of chemoimmunotherapy to both reduce tumor burden and mobilize hematopoietic progenitors is warranted. Finally, any clinical result achieved by this short course of chemotherapy could be consolidated by radioimmunotherapy, followed by high-dose chemotherapy and autologous SCT.

Yet, it is predictable that even after this sequential treatment, some fraction of poor-prognosis FL patients may eventually relapse. To prevent relapse, as many as 3 immunologically oriented strategies are currently available, alternatively involving rituximab,\textsuperscript{86,87} alpha-interferon,\textsuperscript{64} or idiotypic vaccination.\textsuperscript{65} Each of these strategies has pros and cons that need to be taken into consideration. Rituximab is well tolerated and seems not to be associated with the severe infections one might expect in patients with complete B-cell depletion, which tends to last up to 12 months after completing the course of treatment. A few cases of progressive multifocal leukoencephalopathy from rituximab have been reported, however.\textsuperscript{132} No experience has been published regarding patients undergoing rituximab maintenance over more than 2 years, and this fact warrants caution, should maintenance be considered indefinitely.\textsuperscript{133} Alpha-interferon maintenance is effective, particularly in the context of relatively intensive initial chemotherapy and only at a monthly total dose higher than 36 million units.\textsuperscript{64} At this dosage, a considerable percentage of patients prefer to discontinue such maintenance due to the severe side effects.\textsuperscript{64} Idiotypic vaccination is virtually innocuous and seemingly very effective in FL patients who respond to it from an immunologic standpoint, as shown by the first study ever to prove clinical benefit associated with the use of a therapeutic cancer vaccine in humans. In this study, FL patients in first relapse who achieved a second CR through standard chemotherapy without rituximab were subsequently vaccinated; all patients who mounted an idiotype- and/or tumor-specific immune response systematically maintained their second CR for a time statistically significantly longer than the duration of their corresponding first CR obtained through standard chemotherapy with or without rituximab.\textsuperscript{65,66,134} However, idiotypic vaccination is still neither approved nor commercially available. Moreover, further studies are warranted to confirm clinical benefit on large cohorts of patients and to assure that long-term periodic administration of low-dose granulocyte-macrophage, colony-stimulating factor as an immunologic adjuvant with vaccine boosts does not cause any side effect.\textsuperscript{134}

**FUTURE DIRECTIONS**

Despite the impressive biologic and therapeutic progress made in dealing with FL over the last decade,\textsuperscript{9,10} and although a constantly growing number of FL patients now face real opportunities to be cured of their disease, there is still substantial room for improving treatment. Besides, it has to be recognized that even the most advanced prognostic scores cannot predict the future clinical outcome of any newly diagnosed FL patient on an individual basis. Although it seems counterintuitive, the trend toward attempting to improve DFS by means of immunologically oriented maintenance treatments may actually reduce chances to formally prove cure. Indeed, the concept of cure and that of maintenance treatment are as intrinsically at odds with one another as are the concept of cure and that of watchful waiting. Save for the FL cases with a documented spontaneous regression, cure, whenever deemed necessary, should imply treatment first and absence of need for any further therapy later, even maintenance therapy. The absence of a consensus definition of cure for FL, combined with the increasing length of remissions that are being obtained with more aggressive treatment, complicate clinical research in FL. These considerations lead the author to propose an alternative clinical trial endpoint, at least for poor prognosis FL patients as defined by the FLIPI\textsuperscript{50} and by genomic profiling\textsuperscript{37} at diagnosis/relapse or by any other factor that may be found to adversely affect prognosis. The endpoint the author proposes is DFS off all therapy, even maintenance
rituximab. A general observation in FL research is that a patient may achieve clinical remissions with subsequent therapy after initial relapse, but those subsequent remissions become shorter with every course of treatment.66 The author proposes that a novel therapy has demonstrated sufficient antitumor effects and deserves to be tested in previously untreated patients when it can be shown to produce remissions that last significantly longer than the patient’s initial complete remission obtained with standard treatment. In the same patient population, about half and two-thirds of which is expected to die within 5 and 10 years from diagnosis, respectively,37,50 cure might be defined as a subsequent continuous CR both longer than 10 years and at least twice as long as the previous longest CR.

In principle, it seems reasonable to give FL patients with early-stage disease a chance to be cured by involved field RT and, in case of relapse, to reconsider the use of systemic therapy. Currently, the combination of rituximab and chemotherapy is instead the standard of treatment for most newly diagnosed patients with advanced-stage FL. Three ongoing randomized trials (Table 5) will determine whether a single dose of radioimmunotherapy may successfully replace rituximab in first-line treatment and whether there is a subsequent role in this context for rituximab maintenance or retreatment. On the other hand, first relapse after a combination of rituximab and standard chemotherapy may be considered the most informative setting in which to test novel, alternative, or even aggressive and potentially curative treatment options because the response duration to first-line therapy would already be available for a sound comparison in each and every patient.65,110

### Table 5: Published and Ongoing Pivotal Studies in Follicular Lymphoma

| Type of Study | Main Conclusions | Reference |
|---------------|------------------|-----------|
| Retrospective | PFS and OS improve over time | 4         |
| Retrospective | FFS and OS improve over time | 5         |
| Retrospective | FFS and OS improve over time | 6         |
| Meta-analysis | IFN prolongs survival and remissions | 64        |
| Controlled Phase II | Id vaccine prolongs remissions | 65        |
| Phase III | R-FCM improves PFS over FCM | 80        |
| Phase III | R-CHOP improves ORR, TTF, and PFS over CHOP | 82        |
| Meta-analysis | R-DHT improves OS over CHT | 85        |
| Phase III | R maintenance improves PFS and OS in relapsed/refractory patients | 86        |
| Phase III | R maintenance improves PFS in recuring/refractory patients | 87        |
| Phase II | R-CHOP provides lengthy responses (9-year follow up) | 89        |
| Prospective | ASCT provides lengthy responses (12-year follow up) | 91        |
| Phase III | FM improves CR rates but not PFS and OS over CHOP | 103       |
| Retrospective | ASCT provides lengthy responses if TBI is not used | 108       |
| Controlled retrospective | ASCT prolongs remissions | 110       |
| Retrospective | ASCT provides lengthy responses (12-year follow up) | 111       |
| Phase III | ASCT improves PFS over IFN | 114       |
| Phase III | Ibritumomab improves ORR and CR rates over R | 115       |
| Phase II | Tositumomab provides lengthy responses | 121       |
| Phase III | Ibritumomab consolidation improves PFS over observation | 122       |
| Pooled analysis | Tositumomab provides lengthy responses | 123       |

### Table 5: Ongoing Studies

| Type of Study | Name | Comparison |
|---------------|------|------------|
| Ongoing, Phase III | RESORT | R maintenance versus R retreatment |
| Ongoing, Phase III | Southwest Oncology Group S0016 | CHOP + R versus CHOP + 131I-tositumomab |
| Ongoing, Phase III | PRIMA | R maintenance versus observation |

All ongoing trials are being conducted in newly diagnosed patients. Abbreviations: PFS, progression-free survival; OS, overall survival; FFS, failure-free survival; IFN, interferon; Id, idiotype; R, rituximab; FCM, fludarabine, cyclophosphamide, mitoxantrone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ORR, overall response rate; TTF, time-to-treatment failure; CHT, chemotherapy; ASCT, autologous stem cell transplantation; FM, fludarabine, mitoxantrone; CR, complete response; TBI, total-body irradiation; RESORT, Rituximab Extended Schedule or Retreatment; PRIMA, Primary Rituximab and Maintenance.
While waiting for more follow-up data to emerge on the ability of immunologically oriented maintenance treatments to increase the fraction of patients who experience long-term continuous CR, more traditional therapeutic strategies are being revisited in order to further improve their short- and long-term results. Both *ex vivo* and *in vivo* purging is actively pursued in some autologous SCT settings, while reduced-intensity conditioning is increasingly used for allogeneic SCT. A relatively novel chemotherapy agent like bendamustine is being integrated into an old combination, with preliminary encouraging results. Finally, a great number of novel agents potentially useful in FL patients are in the clinical trial pipeline: new chemotherapeutics, *bcl2* small-molecule inhibitors, other monoclonal antibodies, apoptosis-inducing agents, and immunomodulators. Any of these drugs has the potential to match or even improve the extraordinary results of rituximab.

**PATIENT RESOURCES**

The most relevant clinical studies about which patients should be aware are summarized in Table 5 and include pivotal trials already concluded and published, as well as those that are still ongoing. The FL patient community is linked through a number of support groups and Internet chat rooms. There are a number of excellent resources for patient support, including the American Cancer Society (ACS) (www.cancer.org), the American Society of Hematology (www.hematology.org), the Leukemia and Lymphoma Society (www.lls.org), the Lymphoma Research Foundation (www.lymphoma.org), Patients Against Lymphoma (www.lymphomation.org), Lymphoma Coalition (www.lymphomacoalition.org), the National Cancer Institute (www.cancer.gov), and Asociación Española de Afectados por Linfomas (www.aenal.org).

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