



# Clinical Features, Prognosis and Treatment of Follicular Lymphoma

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**Follicular lymphoma constitutes the most frequent indolent lymphoma, well characterized by its clinical presentation related to nodal involvement and its morphologic and biologic features. Some rare locations of extranodal involvement, such as the gastrointestinal tract or skin, were recently further refined. The description of the Follicular Lymphoma International Prognostic Index (FLIPI) represents an important step in identifying patient subgroups with predictable outcome and comparing the results of clinical trials, although its use in clinical practice remains to be established. Analyses of gene expression profiles or constitutive gene variations may also provide additional insights for prognostication in the**

**near future. Furthermore, these data underline the complex interactions between the tumor cells and their microenvironment; recent attempts to translate these findings with immunohistochemical studies remain unable to robustly predict patient outcome. The therapeutic strategies in follicular lymphoma have been transformed by monoclonal antibodies, used alone or in combination with chemotherapy. Treatment options should be adapted to the clinical features at diagnosis and appear to be able to modify the overall survival of some subgroups of patients. Further efforts may focus on strategies that can alter the natural history of this disease.**

## Introduction

Follicular lymphoma is the second most common subtype of lymphoma (although its incidence may be lower in some parts of the world such as Asia) and represents about 20% to 25% of cases of non-Hodgkin lymphomas in the U.S. and Europe. The pathologic diagnosis is quite robust and reproducible. The disease course is usually characterized by a typically indolent clinical course, although most of the patients do relapse after their treatment. The disease is then characterized by recurrent progressions, with shorter intervals in between. Although the various therapeutic strategies developed in the 1980s and early 1990s had little influence on the life expectancy of patients with follicular lymphoma, the event of anti-CD20 monoclonal antibodies have profoundly changed the therapeutic management of such patients.

## Follicular Lymphoma: Clinical Features

### *The common presentation of patients with follicular lymphoma*

Patients with follicular lymphoma typically present with superficial lymph nodes of small to medium size, sometimes unnoticed or neglected by the patients for a prolonged period of time. All common superficial territories can be involved by the disease. In some patients, the first symptoms are more insidious and related to the slow growth of lymph nodes in deep areas, usually in the infradiaphragmatic territories such as the retroperitoneum, the mesenteric, or the iliac areas. In those cases, patients may complain of atypical symptoms while the tumor bulk can be important, with single or confluent lymph nodes. Primary mediastinal involvement is uncommon, as well as isolated splenic en-

largement. The general status of the patient is usually preserved, with few patients presenting with B symptoms or an altered performance status. Primary involvement of extranodal areas is also very uncommon.<sup>1</sup> The bone marrow is involved in 50% to 60% of the cases.

### *Some unusual clinical presentation of patients with follicular lymphoma*

Follicular lymphoma can arise in the gastrointestinal (GI) tract, predominantly in the duodenum or the small intestine,<sup>2</sup> where it can eventually represent the unique site of disease.<sup>3</sup> Lymphoma infiltration may be unifocal or multifocal, and careful immunohistochemical analysis, eventually combined with molecular or cytogenetic studies, helps distinguish this disease from other lymphoma subtypes arising in the GI tract, such as mantle cell or mucosa-associated lymphoid tissue (MALT) lymphomas. The clinical course of these follicular lymphomas does not seem to be distinct from that observed in common nodal follicular lymphoma.<sup>2</sup>

The new World Health Organization–European Organization for Research on Treatment of Cancer (WHO–EORTC) cutaneous lymphoma classification recognizes an entity called “primary cutaneous follicle center cell lymphoma” that includes what was previously known as “cutaneous follicular lymphoma variant” in the WHO classification.<sup>4</sup> Although these cases share some features (cell morphology and growth pattern) with nodal follicular lymphoma, their biology is likely distinct (usual lack of BCL2-IgH gene rearrangement and BCL2 protein expression). Moreover, the clinical outcome is characterized by a very good prognosis, and recurrences, when they occur, are usually restricted to the skin. Therefore, patients with this entity should be managed differently from those with nodal

follicular lymphomas. Some cases of skin dissemination of typical nodal follicular lymphoma do, however, exist (“secondary cutaneous follicular lymphoma”) and should be recognized and treated appropriately.<sup>5</sup>

Other follicular lymphomas that may be considered as peculiar entities with a distinct behavior are those involving the testis<sup>6</sup> and the rare cases of follicular lymphoma encountered in children.<sup>7</sup>

Finally, the concept of “in situ” follicular lymphoma has been recognized in the last years and describes the presence of focal germinal centers containing centrocytes staining strongly for bcl-2 protein in an otherwise normal lymph node.<sup>8</sup> An extended follow-up of those patients presenting with this specifically limited follicular lymphoma is needed to define their optimal management.

#### Recent advances in follicular lymphoma staging

The metabolic imaging techniques using <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (<sup>18</sup>F-FDG-PET) has become increasingly useful in the management of aggressive lymphoma and Hodgkin disease. Its use is also recommended in defining the response to therapy.<sup>9</sup> Despite the frequency of follicular lymphoma, very few studies have specifically addressed the role of <sup>18</sup>F-FDG-PET in this lymphoma subtype. Several reports do clearly indicate that the disease is usually metabolically avid for <sup>18</sup>F-FDG and that the intensity of the radionuclide uptake is independent of histologic grading.<sup>10-12</sup> A preliminary report<sup>13</sup> suggests that <sup>18</sup>F-FDG uptake at the end of treatment is highly predictive of outcome for patients with follicular lymphoma. In this study, the 2-year progression-free survival (PFS) rates were 20% and 90%, respectively, in the CT<sup>-</sup>/PET<sup>+</sup> and CT<sup>+</sup>/PET<sup>-</sup> patients. Prospective studies are urgently needed in this area to formally establish the prognostic value of <sup>18</sup>F-FDG-PET response after treatment, in order to eventually adapt the therapeutic strategy based on the imaging technique.

#### Histologic transformation in follicular lymphoma

In patients with follicular lymphoma, the appearance of a diffused area of large cells in a new biopsy defines histological transformation. This feature is usually—but not systematically—associated with a poor outcome.<sup>14,15</sup> The

clinical factors associated with the risk of transformation (as well as the biology underlying this phenomenon) are not fully characterized. Some reports indicated that early treatment and achievement of a complete response after the first-line therapy were associated with a lower risk of transformation in patients with follicular lymphoma.<sup>16,17</sup>

### Prognostic Factors in Patients with Follicular Lymphoma

#### Clinical prognostic parameters can predict outcome for patients with follicular lymphoma

Several prognostic parameters for follicular lymphomas were identified in the last two decades, that led to the development of some prognostic indexes. The International Prognostic Index developed for aggressive lymphomas was also found to be able of predicting the outcome for patients with follicular lymphoma, but the proportion of patients in the higher-risk categories was usually limited. For these reasons, investigators throughout the world made a large cooperative effort to design a specific index for follicular lymphoma (called FLIPI, for Follicular Lymphoma International Prognostic Index).<sup>18</sup> Based on five simple independent risk factors (hemoglobin < 12 g/dL, serum LDH > upper normal value, Ann Arbor stage III-IV, number of nodal sites > 4, and age > 60 years), the FLIPI enabled the separation of patients into 3 groups (equilibrated in term of size) with distinct survival probabilities (**Table 1**). The index was found to be valid both for younger and older patients. In clinical practice, this index is easily assessable at patient bedside, although the number of nodal areas involved with lymphoma may eventually turn out to be difficult to clearly delineate. Furthermore, age is a leading risk factor in the index and the index does not identify a substantial proportion of young patients with a really poor outcome (only 17% of patients below 60 years are considered to be “high risk,” and their predicted survival exceeds 50% at 8 years). Finally, the FLIPI does not necessarily account for the need for therapy in newly diagnosed patients. For instance, young stage I or II patients with a retroperitoneal tumor bulk, and eventually elevated LDH, will be classified as low risk, while most clinicians will consider this presentation as an indication for therapy. Conversely, some elderly patients with disseminated disease, but without clinical or biological symptoms may be managed with a watch-and-wait approach while they fall in the high-risk category. Indeed, most of the clinical trials designed to assess the role of immunochemotherapy in the first-line setting included 10% to 20% of patients with a low FLIPI,<sup>19-21</sup> while the same proportion of patients with a low tumor burden, usually managed with watch and wait, have a high FLIPI score.<sup>22</sup> Nevertheless, the FLIPI has become a mandatory tool to compare patients across different clinical studies to assess the value of new biological prognostic factors, and its description at patient’s diagnosis should be considered as routine practice.

**Table 1. Prediction of patients with follicular lymphoma outcome based on the FLIPI.**

No. of risk factors*	FLIPI score	Proportion of patients, %	Overall survival	
			at 5 y, %	at 10 y, %
0 or 1	Low	36	91	71
2	Intermediate	37	78	51
3 to	High	27	53	36

\*Factors adversely affecting survival in the FLIPI include age greater than 60 years; Ann Arbor stage III-IV; number of nodal sites greater than 4; serum LDH level greater than the upper limit of normal; and hemoglobin level less than 12 g/dL.

Adapted from Solal-Celigny et al.<sup>18</sup>

### Recent advances in identifying new biological prognostic factors in follicular lymphoma

Classic morphologic parameters identified using the biopsy specimen, such as grading or presence of diffuse areas, were not reproducibly found to be of prognostic significance in different patients series and were not adopted worldwide as standard criteria for patient prognostication. This may be related to the difficulties in reproducing the counts of centroblasts (grade 3 follicular lymphoma being defined by the presence of more than 15 centroblasts per high-power field) and evaluating the presence of diffuse areas, resulting in further difficulties in separating grade 3a from grade 3b.<sup>23</sup> Although some reports indicate that grade 3 follicular lymphoma (whether 3a or 3b) may have a distinct outcome,<sup>24,25</sup> this finding seems to be restricted to patient cohorts treated without anthracyclines. Most clinical trials register patients with grade 1, 2 or 3a, while many investigators consider grade 3b as a distinct entity and manage those patients like diffuse large B-cell lymphomas. Some cytogenetic findings were found years ago to be associated with an adverse outcome in follicular lymphoma,<sup>26,27</sup> but these techniques are not part of the routine management of patients in many centers.

Recent advances in understanding the biology underlying follicular lymphoma prognosis has been enabled by genome-wide analyses of nucleic acids. Using 286 follicular lymphoma specimens to assess gene expression profiling, investigators from the international Leukaemia Lymphoma Molecular Profiling Project (LLMPP) consortium identified two main gene signatures that were independently associated with follicular lymphoma patient survival.<sup>28</sup> The first signature, called “immune response 1,” was associated with a favorable outcome and includes genes encoding T-cell markers, some of them with a known restricted expression among defined T-cell subsets. The signature “immune response 2” was characterized by the presence of genes known to be preferentially expressed in macrophages. A molecular predictor based on these signatures was able to segregate the patient population into four strata with markedly distinct outcomes, and identified a substantial group of patients (25%) with a median survival of 3.9 years (**Table 2**). Another gene expression study, which focused on the risk of histologic transformation and used a different methodologic approach, also pointed to the importance of genes expressed in the immune cell component of follicular lymphoma samples.<sup>29</sup>

These results prompted several investigators to translate these findings using immunohistochemistry to further characterize in biopsy samples the cells present in the microenvironment of follicular lymphoma, with the aim of assessing their prognostic impact. The Vancouver group first reported the adverse prognostic value of a high macrophage content identified by the CD68 staining positivity<sup>30</sup> in a homogeneous series of patients. These results were corroborated by others,<sup>31</sup> and another group<sup>32</sup> further characterized a subset of these macrophages expressing the STAT1

transcription factor as being predominantly associated with a poor outcome. Interestingly, preliminary reports indicate that the adverse prognostic value of CD68 staining was not maintained in patients receiving a combination of rituximab plus chemotherapy and interferon.<sup>31</sup> Other groups analyzed various T-cell markers in order to further define the functional T-cell subpopulation that could be associated with a favorable outcome, as suggested by gene expression data. CD8<sup>+</sup> infiltrating T cells, assessed by immunohistochemistry (IHC) or by flow cytometry, were identified as being associated with a favorable outcome in two independent studies.<sup>33,34</sup> Two other groups identified T cells expressing FOXP3, thought to distinguish the functional “Treg” cell population, as being associated with a favorable outcome.<sup>35,36</sup> These findings are noteworthy given other data suggesting an adverse role for Treg lymphocytes, both in experimental models (assessing the interactions between the lymphoma cells and surrounding immune cells)<sup>37</sup> and in other tumor subtypes.<sup>38</sup> Another T-cell population, expressing the CD57 antigen, also appeared in another study to be associated with adverse prognostic features.<sup>33</sup> Conversely, the Stanford group analyzed a large series of 289 patients with follicular lymphoma and did not find any significant impact of either the CD8 or the CD4 T-cell (as well as the CD4<sup>+</sup>HLA-DR<sup>+</sup> subpopulation) content.<sup>39</sup> Overall, some contradictory results were reported from one study to another. It should be pointed out that these studies were performed using quite heterogeneous patient populations, both in term of size and treatments, and various methodologic approaches. Furthermore, the technical reproducibility of these immunohistochemistry techniques are not yet validated, a prerequisite recently demonstrated to be crucial in diffuse large B-cell lymphomas.<sup>40</sup> As of today, these data should be regarded as investigational and cannot be used to adapt treatment strategies in patients.

Finally, an elegant study recently addressed the influence of the genetic component determining the immune response in patients with follicular lymphoma.<sup>41</sup> The investigators hypothesized that germ-line variations (single nucleotide polymorphisms [SNPs]) found in immune genes could account for the variability of patients with follicular lymphoma survival. Using complex statistical approaches, they were able to identify 4 SNPs (respectively located in the interleukin (IL)-8, IL2, IL12B and IL1RN genes) en-

**Table 2. Prediction of outcome for patients with follicular lymphoma using a gene expression profiling-derived molecular predictor.**

Quartile of survival predictor score	Median survival, y	Estimated overall survival	
		at 5 y, %	at 10 y, %
1	13.6	86	51
2	11.1	86	58
3	10.8	69	54
4	3.9	38	29

Adapted from Dave et al.<sup>28</sup>

abling them to build a strong outcome predictor, with 5-year survival estimate ranging from 96% to 58%. Given the easy access to these techniques, further studies are on their way to eventually confirm and extend these findings in independent patient cohorts.

Altogether, it appears that the clinical behavior of follicular lymphoma is probably dictated by the interactions between the tumor cells themselves (with their underlying genetic acquired alterations) and the lymph node microenvironment (at least partially determined by the host genetic). The exploration of this complex biological network remains difficult and may eventually require distinct complementary approaches that are not presently validated in clinical practice. Today, clinicians should essentially rely on clinically based indexes to assess patients' prognoses and decide the optimal therapeutic strategy.

#### *Outcome improvement in patients with follicular lymphoma*

The classical series of patients with follicular lymphoma reported a median survival from diagnosis ranging from 8 to 10 years.<sup>42</sup> Recent data coming from single centers or cooperative groups suggest that patient prognosis has been improved. For instance, the MD Anderson Cancer Center reported 580 patients with stage IV disease treated from 1972 until 2002<sup>43</sup> with different immunochemotherapy regimens. These investigators reported a marked improvement in 5-year failure-free survival (from 29% to 60%) and overall survival (OS; from 64% to 95%) in this period. Since many confounding factors may undermine the interpretation of single-center historic data, it is interesting to note that these findings were confirmed when considering patients participating in clinical trial with the same inclusion criteria over time<sup>44,45</sup> (C. Sebban et al, submitted for publication). For instance, the Southwest Oncology Group (SWOG) compared patients treated with CHOP or ProMACE-MOPP (with or without interferon) and those receiving CHOP followed by either rituximab or <sup>131</sup>I-tositumomab.<sup>44</sup> The 4-year progression-free survival was found to be 61% in patients receiving monoclonal antibodies after CHOP as opposed to 46% to 48% in previous studies. Four-year OS was also improved, from 69% up to 91%. Of note, the epidemiologic observations<sup>46</sup> performed in the U.S. from 1983 until 1993 also found an outcome improvement for patients with follicular lymphoma in the last 25 years. The median survival evolved from 83 months to 94 months during this period, representing a decrease in the relative risk of death of 1.8% per year. Interestingly, this improvement was predominantly observed in patients with advanced-stage disease and was more substantial in younger patients, who are more likely to receive systemic therapy. Given the period during which this study was conducted, it is unlikely that these findings could be explained by the development of monoclonal antibodies. Hence, it will be interesting to follow up these epidemiologic studies in the next years.

It is therefore important to know whether the prognostic indexes developed with patients treated in the 1980s and 1990s still hold for patients receiving immunochemotherapy. Indeed, the clinical trials that assessed the prognostic significance of the FLIPI score in patients receiving a combination of chemotherapy plus rituximab found that this index retained its discriminating power in this therapeutic context.<sup>20,21,47</sup> For instance, in patients receiving rituximab combined with chemotherapy plus interferon, the 5-year event-free survivals were 64%, 57% and 43% in the low-risk, intermediate-risk and high-risk FLIPI subgroups, respectively (G. Salles et al, submitted for publication).

#### **Follicular Lymphoma Treatment in 2007**

Before the era of monoclonal antibodies, several therapeutic approaches were tested in order to improve patient outcome. In patients with stage III-IV disease, those included the combination of anthracycline with alkylating agents and interferon administration (during chemotherapy or for maintenance), as well as the use of purine analogs or high-dose therapy with autologous hematopoietic cell transplantation. Although the duration of response was eventually prolonged with several of these options, eventually leading to some marginal survival improvements in selected patient subgroups,<sup>46,48,49</sup> none of them had been recommended as a standard for the management of patients. A common opinion was therefore that the initial treatment was unable to alter the ultimate course of the disease. These different therapeutic options were then used for each disease progression over the prolonged clinical course of patients, according to patient characteristics and physician preference. In the last 10 years, early results obtained with monoclonal antibodies or radioimmunoconjugates in relapsing patients and in phase 2 trials prompted investigators to assess the value of these agents in the first-line treatment setting. Results of several randomized trials were published, usually with a 2- to 3-year follow-up, and are currently updated with a more substantial follow-up. Given the large spectrum of data available, this review will only focus on first-line treatment options.

#### *First-line therapy using rituximab alone, as a short course or with maintenance*

Several groups investigated the use of rituximab as front-line therapy in patients with follicular lymphoma. Early results indicated that about three-quarters of the patients responded to a standard weekly 4-dose program, with approximately half of those responders achieving a complete response (CR) to therapy.<sup>50-53</sup> However, when no further treatment was applied, the median time to disease progression was reproducibly found to be between 18 and 24 months. The long-term results of 49 patients with a low tumor burden in one study<sup>54</sup> further indicated that patients achieving a CR had a median time without progression of more than 4 years, and that at least 5 patients were long-term disease free and with a prolonged molecular remission. In order to

improve these results, the Minnie Pearl Cancer Research Network developed programs with repeated rituximab courses consisting of 4 weekly infusions every 6 months for 2 years.<sup>55</sup> The overall response rate was 73% (37% of CR), and the median progression-free survival was 34 months. A randomized study performed by this group further analyzed the potential benefit of this strategy as compared with that of 4 weekly rituximab administrations followed by retreatment at time of progression.<sup>56</sup> This study showed a significantly improved PFS time in the maintenance arm (31 vs 7 months) and patients in this arm were more likely to achieve a durable CR. However, the “duration of rituximab benefit,” defined as the time without the need to start a cytotoxic regimen, was not different between the 2 study arms, suggesting that retreatment with rituximab at time of progression could be as effective as rituximab maintenance. With a 7-year follow-up presented at the last ASH meeting,<sup>57</sup> it was suggested that the patients who had received rituximab maintenance remained “rituximab responders” for a prolonged period of time. The Swiss cooperative group (SAKK) also showed that, in patients having received 4 weekly infusions, a prolonged rituximab treatment (4 additional infusions every 2 months) was able to improve the time without progression.<sup>52</sup> The selection criteria for patients entering these studies were not identical, although most studies included predominantly patients with rather favorable disease characteristics (low tumor burden or low/intermediate FLIPI score patients).

Based on these data, three prospective studies are currently accruing patients to evaluate the benefit of rituximab first-line therapy followed by maintenance. After a course of 4 weekly infusions, the ECOG 4402 study is investigating in responders a prolonged treatment consisting of single rituximab infusions administered every 3 months until pro-

gression versus retreatment. An international study led by the British Lymphoma group is comparing a “watch-and-wait” approach versus 4 weekly rituximab infusions or 4 weekly infusions followed by maintenance every 2 months for 2 years. Finally, the Swiss group is comparing the prolonged administration schedule (4 + 4) versus a prolonged maintenance, administered every 2 months until the patient becomes refractory to rituximab. The results of these trials will be important to better assess the risk-benefit ratio of such strategies, especially when a rituximab maintenance exceeding 2 years is planned. With such long-term follow-up, this study may eventually provide some insights whether or not the prolonged survival of patients with a favorable prognosis can be improved.

#### *First-line therapy using a combination of rituximab plus chemotherapy*

Several randomized studies investigated the combination of rituximab with conventional chemotherapy (**Table 3**). The proportion of patients within each FLIPI score was rather similar in the four studies. However, the control chemotherapy arm was different in each study, and therefore produced different results. A straight comparison of the CVP (cyclophosphamide, vincristine, prednisone) chemotherapy regimen with or without rituximab was performed in the first study.<sup>58</sup> Patients received some form of consolidation with autologous stem cell transplantation or interferon in one study<sup>59</sup> or interferon alone in another one,<sup>19</sup> while in the French study (where patients also received interferon), the number of chemotherapy cycles was divided by 2 in the rituximab-containing arm.<sup>60</sup> Overall, the four studies demonstrated and improvement in response rates, PFS and OS favoring the rituximab-containing arm (**Table 3**).

Another approach was tested within the ECOG 4496

**Table 3. Randomized studies in patients with follicular lymphoma using rituximab plus chemotherapy.**

Reference	Patients within each FLIPI strata, % low/intermediate/high-risk	Median age, y	Follow-up, mo	Median PFS		Estimated PFS in the experimental arm, %	Improvement of overall survival
				Control arm, mo	Experimental arm, mo		
Marcus et al <sup>21,58</sup>	19 /41/40	52	53	15 (CVP)	34 (R-CVP)	50 (at 3 y)	Yes
Hiddemann et al <sup>59*</sup>	14 /41/45	55	18	31 (CHOP)	Not reached (R-CHOP)	80 (at 2 y)	Yes
Herold et al <sup>19†</sup>	7/37/56	59	47	29 (CHOP)	Not reached (R-MCP)	71 (at 4 y)	Yes
Salles et al <sup>60</sup> (updated)‡	19/35/46	61	60	35 (CHVP+I)	Not reached (R-CHVP+I)	53 (at 5 y)	Yes (in high-risk patients)

Abbreviations: PFS, progression-free survival; CVP, cyclophosphamide, vincristine, and prednisone; R-CVP, rituximab plus CVP; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; MCP, mitoxantrone, chlorambucil, and prednisolone; CHVP+I, cyclophosphamide, doxorubicin, teniposide, and prednisone plus interferon

\*CHOP or R-CHOP was followed by autologous stem cell transplantation or interferon.

†MCP and R-MCP were followed by interferon consolidation.

‡CHVP combined with interferon: 12 chemotherapy courses in the control arm versus 6 in the rituximab containing arm.

study,<sup>47</sup> in which patients who did not progress after 6 to 8 courses of the CVP regimen were randomly allocated to no further treatment versus a consolidation consisting of 4 cycles of 4 weekly rituximab infusions administered every 6 months for 2 years. The results of this study demonstrated a significant improvement of 3-year PFS (62% versus 36%, respectively) in the rituximab consolidation arm as compared with the observation arm.

Other studies investigated the role of rituximab consolidation in patients with a molecular detectable bcl2 rearrangement after CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or a fludarabine-mitoxantrone first-line therapy.<sup>61,62</sup> Both studies reported a benefit of this sequential approach.

Altogether, these studies demonstrate that a first-line treatment that combined rituximab with or after chemotherapy was able to improve the outcome of follicular patients. A meta-analysis (including studies for mantle cell lymphomas and relapsing patients) estimated the benefit of this combination in term of risk reduction (hazard ratio) for disease control (0.62) and mortality (0.65).<sup>63</sup> The benefit in OS observed across the studies is noteworthy given the fact that most patients who did not receive rituximab as part of their induction therapy likely received monoclonal antibodies at the time of progression. The improved survival despite this cross-over further supports the fact that these combinations represent a new standard in the first-line treatment of patients with follicular lymphoma. The preference for a chemotherapy regimen containing an anthracycline remains debated; at this time, no formal evaluations of the addition of anthracycline have been performed in the rituximab area.

#### *Front-line therapy using radioimmunoconjugates, alone or after chemotherapy*

The role of radioimmunoconjugates in the first-line treatment of patients with follicular lymphoma has also been investigated, either as single-agent or as consolidation therapy. Kaminski and colleagues reported the front-line use of <sup>131</sup>I-tositumomab in 76 patients<sup>64</sup> with a very high response rate (95%) and three-quarters of the patients achieving a CR. The 5-year PFS was 59% and the toxicity was limited. Although those patients were selected based on their limited marrow infiltration, these results are challenging compared with other trials, including a substantial proportion of low tumor burden patients (**Table 4**).

Other studies evaluated the potential of radioimmunotherapy after either CHOP,<sup>65</sup> fludarabine,<sup>66</sup> or rituximab followed by R-CHOP.<sup>67</sup> Most studies showed an improvement of the response rate and quality after the administration of the radioimmunoconjugates. In the CHOP-tositumomab study, the estimated 5-year OS was 87%, and the PFS was 67%.<sup>65</sup>

Two important prospective studies are therefore comparing radioimmunoconjugates with other options. The U.S. Intergroup trial compares R-CHOP versus CHOP followed by tositumomab. The FIT international study compared the

administration of <sup>90</sup>Y-ibritumomab as an adjuvant therapy in patients responding to a first-line treatment. This study included 414 patients who received different induction regimens, without rituximab for most patients. The first results indicate an improvement of PFS in patients receiving the radioimmunoconjugates (Ton Hagenbeek, personal communication).

#### **Risk-Adapted Therapeutic Strategies in Follicular Lymphoma and Challenges for the Next Years**

The progress in patient stratification and the development of highly efficient and tolerable therapeutic strategies based on monoclonal antibodies should allow us to revisit the usual therapeutic standards in follicular lymphoma and challenge them with new clinical trials in the future years. One can indeed hypothesize that the future strategies, as opposed to previous ones that aimed to provide a better control of a chronic disease, will try to improve the quality of treatment response in order to provide durable complete remissions that can lead towards survival improvement and perhaps cure. Given the long-term survival of these patients, preference should also be given to treatments without long-term risks or side effects. Since biologically derived prognostic factors are not yet available to further identify patients with specific risks or deserving targeted therapeutic options, it is likely that the usual clinical criteria will remain in use for the next few years (**Table 5**).

In the 10% to 15% of patients with truly localized disease, the usual treatment strategy has been radiation therapy, given its alleged potential for cure.<sup>68</sup> The FLIPI was recently reported to be of prognostic value in this category of patients.<sup>69</sup> Still, some groups also tended to manage some of these patients with a watch-and-wait strategy,<sup>70</sup> while others advocate combined modalities.<sup>71</sup> The consensus on radiation therapy is, however, not that firm; in order

**Table 4. Progression-free survival of patients with follicular lymphoma in some selected studies that included a substantial proportion of patients with favorable characteristics.**

Reference	Therapeutic intervention	Median time to progression, mo
72,73	Watch and wait	24 to 32 (time to new treatment)
51,77,53	4 weekly rituximab infusions	18 to 24
77,55,56	4 weekly rituximab infusions followed by maintenance	32 to 36
64	<sup>131</sup> I-tositumomab alone	73
65	CHOP followed by <sup>131</sup> I-tositumomab	> 60
78	Rituximab combined with CHOP	82

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; <sup>131</sup>I, iodine-131

**Table 5. Criteria for starting a cytotoxic treatment in patients with follicular lymphoma.**

<b>Adapted GELF criteria (FL2000 and PRIMA studies): any one of these criteria</b>	<b>BNLI criteria:<sup>73</sup> any one of these criteria</b>
High tumor bulk defined by either: <ul style="list-style-type: none"><li>– a tumor &gt; 7 cm</li><li>– 3 nodes in 3 distinct areas each &gt; 3 cm</li><li>– symptomatic splenic enlargement</li><li>– organ compression</li><li>– ascites or pleural effusion</li></ul>	Rapid generalized disease progression in the preceeding 3 months
Presence of systemic symptoms	Life threatening organ involvement
ECOG performance status >1 *	Renal or macroscopic liver infiltration
Serum LDH or $\beta$ 2-microglobulin above normal values	Bone lesions
	Presence of systemic symptoms or pruritus
	Hemoglobin < 10 g/dL or WBC < $3.0 \times 10^9/L$ or platelet counts < $100 \times 10^9/L$ ; related to marrow involvement

\*Used in the FL2000 but not in the PRIMA study, given the low percentage of patients with this sole criteria in the former studies (G. Salles, personal communication).

to combine active systemic and localized treatment, it may then be worth assessing the value of monoclonal antibodies (alone or combined with radiation therapy) or radioimmunoconjugates in these patients.

Some other patients with advanced stages of the disease fulfill the usual criteria for delaying treatment and, based on the results of former randomized trials,<sup>72,73</sup> were usually managed with a “watch-and-wait” strategy. However, given the potential discomfort of dealing with an untreated cancer without therapy, physicians and patients may currently prefer to start earlier a treatment with limited toxicity in these patients, even if no long-term benefit is established. It is, however, still unknown whether early treatment with rituximab is completely safe, both in terms of infectious toxicity (when maintenance is used) and in terms of potentially induced resistance to the antibody. It is necessary to further evaluate this attitude, and this patient population is at this time targeted by studies using noncytotoxic agents, for instance, rituximab, as is the case in the SAKK, ECOG 4402 and British Lymphoma Group trials. Nevertheless, it is quite uncertain whether these studies will be able to demonstrate an OS benefit with such strategy. Given the improvement of survival obtained with immunochemotherapy and some impressive results of radioimmunoconjugates in the first-line setting, one can propose the development of clinical studies aimed to evaluate shorter immunochemotherapy- or radioimmunotherapy-based schedules,<sup>74</sup> with or without rituximab maintenance. Those studies may then have the presumed goal of altering the clinical course of the disease.

Finally, despite the progress observed in recent years, the prognosis of patients (especially young ones) with adverse features remains unsatisfactory. As immunochemotherapy nowadays represent a standard of care for these patients, open questions are related to the improvement of rituximab-chemotherapy based classic schedules. Based on the benefit of rituximab maintenance observed in relapsing patients,<sup>75,76</sup> an international collaborative study coor-

inated by the GELA (the PRIMA study) is currently evaluating the benefit of a 2-year rituximab maintenance after rituximab plus chemotherapy. More than 1200 patients have been currently registered, and the first interim analysis may be carried out in 2008. Other options for consolidation after immunochemotherapy may be represented by high-dose therapy supported by autologous hematopoietic cell transplantation (as proposed recently in the RiCHOP study conducted by the German Low Grade Study Group) or radioimmunotherapy. Other approaches may rely upon new agents that could increase the response rate and quality obtained with rituximab plus chemotherapy, if these compounds do not present a substantial toxicity. Finally, other approaches using the immune response obtained after vaccination should also be investigated.

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