

First-Line Treatment of Follicular Lymphoma in the Era of Monoclonal Antibodies

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Abstract: This review describes the recent evolution in the first-line treatment of patients with follicular lymphoma. In cases without adverse prognostic parameters, delayed treatment still is the best option. The combination of rituximab plus chemotherapy in patients with adverse prognostic parameters is the treatment associated with the highest complete response rates and the longer time to progression compared to chemotherapy or rituximab alone. The best chemotherapy regimen is not yet described. Also yet to be described is the place of radioimmunotherapy versus rituximab plus chemotherapy. High-dose therapies with autologous stem-cell transplant have a place in the treatment of these patients but not in first line.

Follicular lymphoma (FL) is characterized by a proliferation of CD10(+) centrocytic and centroblastic cells, with t(14;18) and/or bcl-2 gene rearrangement in greater than 80% of them. It represents 20–25% of all lymphomas, depending on geographic region. Patients may be asymptomatic with slowly progressive lymphadenopathy or present with symptomatic complications of progressive tumor growth requiring treatment. Clinically, it is characterized by a nodal proliferation with bone marrow involvement present in more than 70% of patients. Extranodal locations are rare at diagnosis but characterize refractoriness to treatment or transformation into an aggressive lymphoma.¹ In nearly all cases, despite responsiveness to treatment, patients eventually relapse. Despite improvements in therapy during the last 20 years, there has been no agreed-upon standard, primarily because response to first-line treatment seems not to influence the overall survival of these patients. Treatment options are diverse, ranging from observation to bone marrow transplantation. The addition of rituximab (Rituxan, Genentech/Biogen IDEC) and radiolabeled monoclonal antibodies to our therapeutic tools has completely changed the therapeutic possibilities and may lead to the standardization of treatment as in diffuse large B-cell lymphoma.²

Diagnosis

In a great majority of cases, the first symptoms of disease are the appearance of 1 or more peripheral lymph nodes. Diseased abdominal lymph nodes lead to abdominal pain, diarrhea, or constipation.

Keywords

Follicular lymphoma, rituximab, first-line therapy, R-CHOP, radioimmunotherapy

Involvement of the bone marrow is present in 70% of cases, but other extranodal locations are rare at diagnosis and generally occur when the lymphoma progresses or transforms into an aggressive one. Cutaneous or gastrointestinal involvement at presentation is rare.^{3,4}

Diagnosis is made by lymph node biopsy, which optimally requires review by an expert hematologist. Cell size and growth pattern morphology are characteristic and allow the categorization of patients into grade 1, 2, and 3 subgroups based on the percentage of large cells, using the current World Health Organization classification system.⁵ Except for grade 3B, which features large sheets of diffuse infiltration of large cells and is considered a diffuse large-cell lymphoma, this grading system is not completely reproducible from one pathologist to another and is not associated with therapeutic implication. Immunophenotyping should always be done and reveals the expression of B-cell differentiation antigens, including bright expression of CD20, CD19, and CD10 and absent co-expression of CD5. Staining for the bcl-2 protein is nearly always positive. Cytogenetic analysis reveals the characteristic t(14;18) translocation, resulting in unregulated expression of the bcl-2 protein.

Staging

Clinical staging of newly diagnosed patients includes a thorough physical examination, routine complete blood count and blood chemistry, and measures of β 2-microglobulin and lactic dehydrogenase (LDH) levels. Computerized tomography (CT) scans of the chest, abdomen, and pelvis are mandatory. A bone marrow biopsy should be examined by routine pathology and evaluated using flow cytometry and usually molecular pathology of immunoglobulin H gene rearrangements and t(14;18) translocation. When positive, these tests can be used to provide molecular monitoring after therapy and for monitoring of complete remissions in clinical trials. Newer imaging modalities including positron emission tomography (PET) scans or combination CT/PET will likely provide future advances by identifying patients with residual active disease following completion of standard treatment. However, the value of such scans for prediction of relapse is not as well defined as in more aggressive lymphomas.⁶

Prognostic Factors

Until recently, factors associated with a poor outcome were those associated with a high tumor mass: involvement of numerous lymph node areas with lymph nodes larger than 3 cm, 1 or more lymph nodes larger than 7 cm, presence of B symptoms (fever, weight loss, night sweats), poor performance status, high LDH or β 2-microglobulin level,

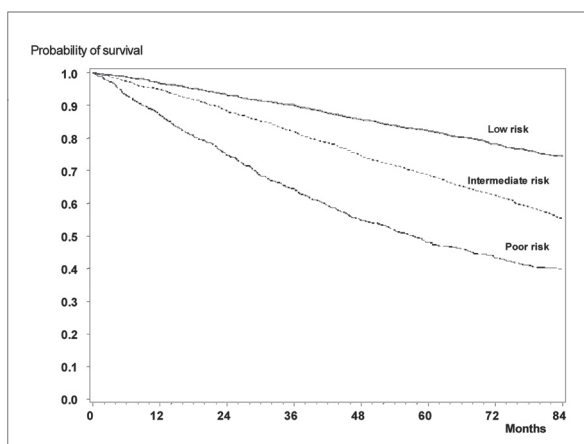


Figure 1. Three risk groups as defined by the Follicular Lymphoma International Prognostic Index (adapted from Solal-Celigny et al⁷).

extranodal sites other than bone marrow, and cytopenia. In various lymphomas, these factors have been used to separate patients who require treatment at diagnosis from those whose treatment may be delayed.

A large international group has recently developed the Follicular Lymphoma International Prognostic Index (FLIPI)⁷; the index was developed using 1,795 patients who were treated 10 years ago—before the era of rituximab—so its validity for patients treated with rituximab needs to be demonstrated. The FLIPI consists of 5 parameters: age (>60 years vs \leq 60 years), Ann Arbor stage (III–IV vs I–II), hemoglobin level (<12.0 g/dL vs \geq 12.0 g/dL), number of nodal areas (>4 vs \leq 4), and serum LDH level (elevated vs normal or below). The group defined 3 risk groups (Figure 1): low risk (0–1 adverse factor, 36% of patients), intermediate risk (2 factors, 37% of patients, hazard ratio [HR]=2.3), and poor risk (\geq 3 adverse factors, 27% of patients, HR=4.3). The FLIPI allows for comparison of patient characteristics from different studies, and thus for a comparison of results. However, it does not identify those patients for whom delayed treatment is the best option. Also, patients who have a very poor prognosis and need intensive treatment at diagnosis are not identified by the FLIPI because they do not correspond to a FLIPI score greater than 3. These patients are characterized by a large tumor mass with a high LDH level, and thus may have a score of 1 in the FLIPI, which is low risk. Thus, in therapeutic trials, the characterization of patients requires other criteria. For example, the 2 current European trials in patients with FL, the PriMa trial in patients requiring treatment and the RWW trial in patients not requiring initial treatment, used the criteria described in the GELF study.^{8,9}

Biologic parameters may be useful in predicting outcome, as recently demonstrated in several pilot studies.¹⁰⁻¹² However, it has not yet been possible to incorporate these new biologic parameters into large multicenter prospective randomized studies because of the complicated structure and the money necessary to fund such studies. Until pilot retrospective studies have defined the most interesting biologic parameters, they will have little importance in the treatment of patients with FL.

Localized FL

Clinically, FL may be localized to 1 lymph node in 1 site or 2 contiguous sites; however, localized disease may also be more disseminated, involving more than 1 lymph node or more distant sites, such as inguinal, lumboarctic, or right and left cervical nodes. The quality of the bone marrow biopsy is important, and bcl-2–rearranged cells are often present in blood and bone marrow, even when the disease seems localized. Patients with such widespread localized disease must be considered to have disseminated disease, and treatment depends on the presence of adverse parameters (see below).

Truly localized disease exists when just 1 cervical or inguinal lymph node is involved. Usually, the size of the tumor is small, but if it is large (>7 cm) treatment with chemotherapy is needed as in patients with disseminated disease. Radiotherapy alone has been used in patients with nonbulky stage I or II disease outside randomized study (Table 1). Good results have been reported, but median survival is only approximately 50% at 15 years. For localized indolent lymphoma this may not be considered acceptable and treatment should be reevaluated according to current medical thinking: no initial treatment, then chemotherapy at time of progression. In a recent long-term follow-up study of patients who received no initial therapy, 63% of patients with localized disease had not been treated 86 months after diagnosis.¹³

Approximately 20% of FL patients have localized disease without bulky tumor. In such patients, targeted radiotherapy achieves complete remission in over 95% of cases and relapse-free 10-year survival in 50% of cases. However, the probability of cure is very low because there is no plateau in the survival curve and most patients relapse.

Figure 2 shows long-term survival rates observed in our department for 154 patients with stage I or II FL. Sixty percent of our patients had progressed 10 years after the initial treatment. These results may well be improved in the future, if chemotherapy plus monoclonal antibodies are included in the treatment of such patients. No randomized data currently exist supporting the use of adjuvant chemotherapy, but thus far only 1 trial of low-intensity chemotherapy has been sufficiently powered to

Table 1. Survival Data for Localized Disease Treated With Radiation Only

Series	Stage	N	Freedom-From-Relapse Survival, %	Overall Survival, %
Princess Margaret Hospital ⁴⁴	I, II	525	53	58
BNLI ⁴⁵	I/IE	208	49	64
Royal Marsden Hospital ⁴⁶	I, II	58	43	79
Stanford ⁴⁷	I, II	177	44	64
M. D. Anderson Cancer Institute ⁴⁸	I, II	80	66/26	45

BNLI = British National Lymphoma Investigation.

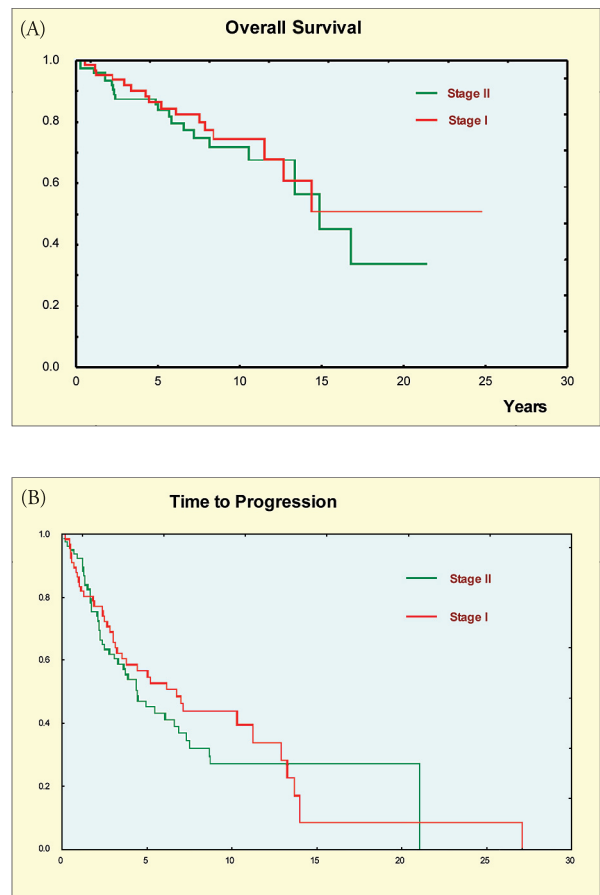


Figure 2. Overall survival (A) and time to progression (B) in 154 patients with localized follicular lymphoma treated in our center (stage I, 71 patients, stage II, 83 patients).

address the question. Nevertheless, data from a large phase II study from the University of Texas M. D. Anderson Cancer Center suggest that combined chemotherapy and radiation therapy can produce progression-free survival (PFS) results that are far superior to historical series, with survival at 10 years approximately 20% higher than radiation alone.^{14,15} No data have yet been presented for the combination of chemotherapy and rituximab.

Delayed Treatment

Patients presenting without adverse parameters do not require immediate treatment.^{16,17} Three randomized studies have shown an identical survival for these patients whether treated or untreated.^{18,19} The criteria for allocating a patient to so-called “watch and wait” therapy—in which treatment is delayed until signs of progression or appearance of adverse parameters—were not identical in these trials, but there is now an agreement on what criteria should be used: absence of large tumor mass, absence of B symptoms, tumor smaller than 7 cm in diameter, fewer than 3 nodes larger than 3 cm, no organ compression or effusion, and normal LDH and β 2-microglobulin levels. These criteria are being used in the RWW study, which compares treatment with rituximab to no treatment.

Several phase II studies have been conducted in these patients to see if early treatment with rituximab or ¹³¹I-tositumomab further delays the need for chemotherapy, is associated with a higher molecular remission, and possibly cures some patients.²⁰⁻²² The results of these studies were somewhat disappointing because the PFS did

not increase. Monoclonal antibodies alone induced a high response rate, with 40–75% complete response (CR), and, in some patients, a molecular response. However, most patients progressed between 24 months and 4 years after the end of treatment, a result similar to that observed with delayed therapeutic intervention. Currently, there is no indication that early therapeutic intervention in patients with low tumor mass will prolong survival. Therefore, the current standard approach remains “watch and wait.”

Patients Requiring Treatment

Patients with adverse parameters at diagnosis or after a period of watchful waiting need to be treated. Currently, there is no universally accepted standard therapy. Proposed treatments include standard chemotherapy (single-agent or multidrug regimens with or without doxorubicin or with fludarabine), chemotherapy plus interferon (IFN), high-dose therapy (HDT) followed by autologous stem cell transplantation, and active immunotherapy (vaccine). Below we review the risks and benefits of each of these options.

Conventional Chemotherapy: Results have varied considerably in studies of conventional chemotherapy with similar regimens, although the differences are probably more related to the type of patients included in the trials than the regimens (Table 2). Comparison is difficult because even though they were all randomized studies, patient characteristics differed and none reported results using FLIPI parameters. However, fludarabine alone,

Table 2. Survival and Response Data From Randomized Studies of First-Line Therapy for Follicular Lymphoma

Regimen	References	CR Rates, %	Median Progression-Free Survival	Median Overall Survival
Chlorambucil/ cyclophosphamide	Peterson ⁴⁹	66	4.2 yr	8.7 yr
	Baldini ⁵⁰	34	30 mo	>38 mo
Fludarabine	Coiffier ⁵¹	34	1.5 yr	2.7 yr
	Hagenbeek ⁵²	38	21 mo	Not reached
CVP	Klasa ⁵³	7	9 mo	44 mo
	Hagenbeek ⁵²	15	15 mo	Not reached
	Marcus ⁵⁴	10	15 mo	>30 mo
CHOP	Zinzani ⁵⁵	51	>3 yr	>3 yr
	Peterson ⁴⁹	60	3.6 yr	9.7 yr
FM	Zinzani ⁵⁵	68	>3 yr	>3 yr
	Foussard ⁵⁶	49	3 yr	>53 mo
CHVP+INF	Solal-Celigny ⁹	20	2.9 yr	>6 yr

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CHVP = cyclophosphamide, doxorubicin, teniposide, prednisone; CR = complete response; CVP = cyclophosphamide, vincristine, prednisone; FM = fludarabine, mitoxantrone; IFN = interferon.

chlorambucil alone, and CVP (cyclophosphamide, vincristine, and prednisone) seem to be associated with lower CR rates and a shorter time to progression than CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or fludarabine combinations. Most of these studies were reported too early to have significant figures for overall survival. Because of the benefit of rituximab in this disease (see below), these studies should be repeated with the combination of rituximab and chemotherapy.

Interferon: A CHOP-like regimen combined with IFN was the only regimen that was associated with survival improvement in randomized studies.^{9,23} This benefit was notable because of the toxicity of IFN and the absence of benefit in studies using low doses of IFN (<3 million units 3 times a week) or when combined with a regimen that did not include doxorubicin. However, a recent meta-analysis has confirmed a significant survival advantage with IFN- α 2.²⁴ This advantage was seen when IFN- α 2 was given (1) in conjunction with relatively intensive initial chemotherapy, (2) at a dose \geq 5 million units, (3) at a cumulative dose \geq 36 million units per month, and (4) with chemotherapy rather than as maintenance therapy. For remission duration, there was also a significant advantage in favor of IFN- α 2, irrespective of the intensity of chemotherapy, IFN dose, or whether IFN was given as a maintenance strategy or with chemotherapy.

Because of the specific toxicity of IFN and its lower safety/efficacy ratio compared to rituximab, this drug is rarely used for the treatment of patients with FL.

High-dose Therapy and Autologous Stem-Cell Transplantation: Because of its efficacy in relapsing patients,²⁵ HDT followed by autologous stem cell transplantation was proposed as first-line treatment in patients with a high risk of failure.²⁶⁻²⁸ Three randomized studies showed a benefit for HDT despite a different comparator in each study. However, this benefit was less important in the GELA studies and associated with secondary leukemia in the GOELAMS study. In the GOELAMS study, the risk of secondary myelodysplasia or leukemia was associated with the ex-vivo purge of stem cells. Other studies using no purge or in-vivo purge with rituximab have a less severe risk. Because of the higher toxicity rates associated with HDT and the high efficacy of rituximab, this treatment is currently reserved for relapsing patients. However, if combined with rituximab it might be associated with a very long PFS in patients with a high risk of progression and/or transformation. Such an indication needs to be evaluated in randomized studies.

Allogeneic transplantation is not recommended for untreated patients. Its current recommended indication is in patients relapsing after HDT and autologous transplantation.

Vaccine: Active immunotherapy involves the generation of immune responses against the idiotype expressed by the tumor clone. The efficacy of this therapy is enhanced by the addition of granulocyte-macrophage colony-stimulating factor and coupling the idiotype protein to keyhole limpet hemocyanin. In situations where the tumor clone is minimal, such as after chemotherapy, active immunotherapy was associated with tumor responses.²⁹ Ongoing phase III trials are being conducted to determine definitive evidence of its role in patients with FL.

The Benefits of Rituximab

Initial studies with rituximab were done in patients with relapsing or refractory indolent lymphomas, mostly follicular.³⁰ These data demonstrated the efficacy of rituximab and its safety in patients already treated with multiple chemotherapy regimens. Because of its low toxicity, rituximab has also been used in with low-risk FL, but this approach is not currently recommended (see above).²⁰

Rituximab Monotherapy: The efficacy of single-agent rituximab has been studied in patients with an aggressive presentation requiring treatment at diagnosis or after a period of observation.^{21,31,32} The response rate after 4 infusions was not significantly higher than in relapsing patients: around 50%, with less than 10% CR. Progression occurred in less than 12 months in more than 50% of these responding patients. However, prolonged rituximab treatment with repeated infusions led to increased response rates, particularly CR rates. In a study conducted by Hainsworth and associates that compared rituximab maintenance therapy every 6 months for 2 years with re-treatment at progression, the CR rate increased by 20% with a stable partial response (PR) rate, meaning that more patients responded with longer treatment.³¹ The duration of response was longer with rituximab maintenance therapy, but the time without chemotherapy was identical in the 2 groups. A Swiss study included patients receiving rituximab for first-line therapy and for relapse.³³ With only 4 extra injections of rituximab every 2 months, the time to progression was doubled from 19 months to 36 months.

The consensus from these studies is that prolonged treatment increases the response to rituximab compared to the standard 4-week schedule, but does not prolong the duration of rituximab benefit or time without chemotherapy compared to re-treatment at demand. Therefore, longer initial treatment or re-treating these patients appears to be of equal benefit, and both are acceptable for the patients; however, prolonged treatment is not approved by regulatory authorities in the United States or Europe, and might be more expensive than re-treatment. Both studies only included patients treated with rituximab before maintenance/re-treatment, and therefore these

conclusions might not be true for patients who received an initial combination of rituximab and chemotherapy (see below). Moreover, neither study had the statistical power to draw conclusions in first-line patients.

Rituximab Combined with Chemotherapy: In the first phase II study of a combination of chemotherapy (CHOP) and rituximab, rituximab was interspersed between CHOP cycles.³⁴ This schema showed a high efficacy in a group of selected patients, with 100% of them responding to treatment, a median PFS of 82 months, and median survival longer than 9 years. Several randomized studies have now demonstrated that the addition of rituximab to standard first-line chemotherapy regimens results in higher response rates, longer time to progression, and longer event-free survival versus the same regimens without rituximab (Table 3). Four studies have reported a benefit in terms of CR rates and PFS, although follow-up thus far is too short to detect an overall survival benefit.³⁵⁻³⁸ The first study randomized patients between 8 cycles of CVP or rituximab plus CVP (R-CVP). Overall response rates and CR rates were 81% and 41% in the R-CVP arm versus 57% and 10% in the CVP arm, respectively ($P < .0001$). At a median follow-up of 30 months, patients treated with R-CVP had a highly significantly prolonged time to progression (median 32 months vs 15 months for CVP; $P < .0001$). Median time to treatment

failure was 27 months in patients receiving R-CVP and 7 months in the CVP arm ($P < .0001$).³⁵ Overall survival is not yet different. In the second study, patients were randomized to 6 cycles of CHOP or rituximab plus CHOP (R-CHOP).^{36,39} In 428 patients, R-CHOP revealed a significantly higher response rate (96% vs 90%, $P = .011$) and a longer time to treatment failure (median not reached vs 2.6 years, $P < .0001$) than CHOP alone. In this study, the CR rate was artificially low but not truly evaluated before the second randomization because the bone marrow evaluation was not scheduled. Therefore, all patients with bone marrow involvement at diagnosis were counted as partial responders. In the third study, patients with indolent lymphoma (56% follicular) were randomized to 6 cycles of MCP (mitoxantrone, chlorambucil, and prednisolone) and rituximab plus MCP (R-MCP).³⁷ The overall response rates and the CR rates for all patients were 85.5% and 42% in the R-MCP arm versus 65.5% and 20% in the MCP arm, respectively ($P < .0001$). Event-free survival was significantly prolonged for patients receiving R-MCP versus MCP alone ($P < .001$). Median event-free survival for MCP was 19 months and not reached for R-MCP. Follow-up was too short in these last 2 studies for determining overall survival. In the fourth study, patients were randomized to 18 months of treatment with CHVP + INF or rituximab plus CHVP (R-CHVP) + INF.³⁸ The first analysis demonstrated a significantly improved

Table 3. Response and Survival Data From Randomized Studies of Rituximab + Chemotherapy vs Chemotherapy Alone

Setting	Response Rates, %	CR Rates, %	Event-Free Survival, mo	Time to Progression, mo	Overall Survival
First-Line Patients					
Marcus ³⁵ R-CVP vs CVP	81 57*	41 10*	27 7*	32 15*	Not different
Hiddemann ³⁶ R-CHOP vs CHOP	97 90	20 17	68 21*	50 15*	Not analyzed
Salles ³⁸ R-CHVP+IFN vs CHVP+IFN	Not analyzed	79 63*	Not reached	Not reached	Not analyzed
Herold ³⁷ R-MCP vs MCP	85.5 65.5*	42 20*	Not reached 19*	Not reported	Not reported
Adjuvant Rituximab in First Line					
Hochster ⁴⁰ R-CVP vs CVP (maintenance)	Not reported	30 22†	Not reported	4.2 yr 1.5 yr*	Trend in favor of R

* $P < .01$

† $P < .05$

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CHVP = cyclophosphamide, doxorubicin, teniposide, prednisone; CR = complete response; CVP = cyclophosphamide, vincristine, prednisone; MCP = mitoxantrone, chlorambucil, prednisolone; R = rituximab.

response to therapy with R-CHVP + IFN versus CHVP + IFN, at both 6 months (CR + unconfirmed CR [CRu] 49% vs 76%; PR 36% vs 18%, respectively [$P < .0001$]); and 18 months (CR + CRu 79% vs 63%; PR 5% vs 10%, respectively [$P = .004$]). Estimated event-free survival at 2.5 years is 62% with CHVP + IFN versus 78% with R-CHVP + IFN ($P = .003$). Finally, 1 study reported that maintenance with rituximab in patients treated with chemotherapy increased CR rates and prolonged PFS.⁴⁰ However, the role of rituximab maintenance after a combination of rituximab plus chemotherapy has not yet been evaluated, so it is not recommended as a standard treatment.

These studies have demonstrated the benefit combining rituximab with chemotherapy as standard treatment for FL patients requiring therapy. It has not yet been determined which of these regimens is superior, but a comparison of CR, event-free survival, and PFS rates from the different studies seems to indicate a greater benefit with the R-CHOP regimen. A comparison of results obtained with R-CHOP versus those obtained with rituximab alone also favors the use of R-CHOP. However, this conclusion needs to be considered with caution because no randomized study has yet compared these different regimens and data for overall survival are not yet known.

Radioimmunotherapy

Two monoclonal antibodies have been combined with a radionucleotide and approved for the treatment of relapsing/refractory FL. Radioimmunotherapy with yttrium (Y)-90- and iodine (I)-131-labeled anti-CD20 antibodies (ibritumomab tiuxetan [Zevalin, Biogen Idec] and tositumomab [Bexxar, GlaxoSmithKline], respectively) was associated with a high response rate in relapsing/refractory patients.^{41,42} Ibritumomab was not tested in untreated FL patients.

Tositumomab following CHOP chemotherapy in previously untreated patients was investigated by the Southwest Oncology Group (SWOG).⁴³ In this group of 90 patients the overall response rate to CHOP plus tositumomab was 90% with 67% CR. Of patients not in complete remission after CHOP, 57% improved their response after tositumomab. Estimated 2-year PFS was 81%. SWOG is currently conducting a study comparing tositumomab and rituximab in FL patients treated with CHOP as first-line treatment. Kaminski and colleagues recently presented the results of a phase II trial evaluating tositumomab as initial treatment in patients with FL.²² Of the 76 patients enrolled, more than half lacked criteria associated with poor outcome and therefore would not ordinarily be treated. CR was observed in 75% of the patients but only in 58% of those with a large lymph node. Median PFS was 6.1 years for all patients but less

for patients with criteria associated with poor outcome (details not given in the manuscript). In summary, this study showed that patients without a large tumor may respond well to tositumomab, but it did not allow evaluating the role of this drug in patients with FL. Lacking information on overall survival rates, and given the toxicity associated with tositumomab in relapsing/refractory patients, no recommendation is made for using it in untreated patients.

Other Monoclonal Antibodies

Several monoclonal antibodies directed against CD20 (hA20, HuMax-CD20, eculizumab [Alexion Pharmaceuticals]) or other antigens (epratuzumab [Immunomedics] for CD22, apolizumab [Remitogen, Protein Design Labs] for HLA-DRB chain, galiximab [Biogen IDEC] for CD80) are currently in phase I or II trials. No definitive conclusion can be made regarding on their activity, toxicity, and benefit compared with rituximab in first-line patients. The real interest of these new antibodies will have to be demonstrated in randomized studies and by comparison with rituximab.

Conclusions

The treatment of patients with FL has been completely modified by the development of rituximab. No initial therapy is still the recommended option for patients without adverse prognostic parameters at diagnosis. A combination of rituximab and chemotherapy is recommended for those with adverse prognostic parameters. Maintenance with rituximab needs to be evaluated after rituximab plus chemotherapy. HDT after rituximab plus chemotherapy might be indicated in patients with advanced disease but this is still speculative. Other options such as radioimmunotherapy, vaccine, or nonmyeloablative stem cell transplantation need to be evaluated in randomized studies before being proposed outside clinical trials. With the development of these new prospects, this long-thought-incurable lymphoma may have curative options, at least in a subset of patients.

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