Follicular Lymphoma

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Abstract

Follicular lymphoma is the most common and well-characterized low-grade lymphoma.

Gene expression profiling and biomarker development have improved our understanding of its biology, but there remains no robust biologic, immunohistochemical prognostic marker at diagnosis. Therefore, clinical criteria such as the Follicular Lymphoma International Prognostic Index (FLIPI) and the GELA/BNLI criteria for starting treatment remain the most useful tools to both assign prognosis and commence therapy.

Our better understanding of the heterogeneity of follicular lymphoma is paralleled by the development of a plethora of new first-line treatment options using monoclonal antibodies, either alone or in combination with chemotherapy or radio-conjugates. Emerging data supports the influence of depth of response to first-line therapy on long-term outcomes, and there is early evidence suggesting that rituximab maintenance therapy prolongs both progression-free and possibly overall survival. Improved patient understanding of this usually chronic and incurable disease is increasingly associated with a willingness to participate in treatment decision making. Thus, the selection of therapy at each phase of the disease, with subsequent impact on future therapeutic options, becomes a more sophisticated individualized process.

Keywords

Follicular lymphoma • FLIPI index • Tumor burden • Watch and wait strategy • Rituximab plus chemotherapy • Rituximab maintenance • Radioimmunotherapy • Autologous transplant • Patient participation to treatment decision

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A. Younes, B. Coiffier (eds.), *Lymphoma*, Current Clinical Oncology, Vol. 43,
DOI 10.1007/978-1-62703-408-1_9,

Introduction

Follicular lymphoma, the second most common subtype of lymphoma, represents up to 25 % of non-Hodgkin lymphomas in Europe and the USA. The pathological diagnosis is robust and generally reproducible, noting the more recent exclusion of Grade 3b disease (diffuse areas containing >15 centroblasts per hpf without admixed centrocytes) from the common spectrum of follicular lymphoma. The disease course, typically indolent both at diagnosis and at relapse, is characterized by recurrent progression with shorter remissions. The appearance of a diffuse area of large cells in a new biopsy defines histological transformation, a feature usually associated with a poor outcome [1, 2] occurring in a variable number of patients.

Follicular lymphoma patients typically present with superficial lymphadenopathy, at times neglected by the patient for a prolonged period. In some patients, the first symptoms are related to the insidious growth of deep abdominal lymphadenopathy. Impaired performance status or B symptoms are uncommon. Nonetheless, the majority of patients, 70–85 %, have advanced-stage disease, with bone marrow involvement in 50–60 %.

Prognostic Factors

The FLIPI (Follicular Lymphoma International Prognostic Index [3]) is based on five simple independent risk factors (hemoglobin <12 g/dL, serum LDH > upper normal value, Ann Arbor stages III-IV, number of nodal sites >4, age >60 years). A robust prognostic indicator, the FLIPI separates newly diagnosed patients into three equal-sized groups with distinct survival probabilities (Table 9.1) [3]. The index is valid for both younger and older patients and retains its discriminating power in the context of combination chemotherapy plus rituximab [4–6] (Fig. 9.1). However, it does not identify a significant minority of patients with a really poor outcome for whom a more aggressive therapy may be considered. For instance, while 17 % of patients <60 years are categorized as "high-risk FLIPI," their predicted survival is still >50 % at 8 years. Finally, the FLIPI does not necessarily dictate a need for therapy. Young stage I or II patients with retroperitoneal tumor bulk, and elevated LDH, will be classified as low risk, yet most clinicians consider this presentation an indication for therapy. Conversely, a watch and wait approach is appropriate for many elderly patients with disseminated disease lacking systemic symptoms despite a high FLIPI. Most clinical trials assessing the role of frontline immunochemotherapy included 10–20 % of patients with a low FLIPI [4, 7, 8], while the same proportion of patients with a low tumor burden managed with watch and wait have a high-FLIPI score [9].

An interesting recent development has been that of the FLIPI2: a prognostic index developed for follicular lymphoma patients receiving immediate therapy using progression-free survival as the principal endpoint [10]. Again comprising five factors—$\beta_2$microglobulin > normal, longest diameter of the largest involved node >6 cm, bone marrow involvement, hemoglobin <12 g/dL, and age older than 60 years—the

Table 9.1 Prediction of follicular lymphoma patients' outcome based on the FLIPI

Number of risk factors[a]	FLIPI score	Proportion of patients (%)	Overall survival (%)	
			At 5 years	At 10 years
0 or 1	Low	36	91	71
2	Intermediate	37	78	51
3 to	High	27	53	36

Adapted from Solal-Celigny et al. [3]; used with permission

[a]Factors adversely affecting survival in the FLIPI include age greater than 60 years, Ann Arbor stages 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

FLIPI2 identifies a 3-year PFS rate of 91, 69, and 51 % for patients at low, intermediate, and high risk, respectively ($p<0.0001$). This prospectively collected and externally validated series highlights the predictive power of β_2-microglobulin and a single lymph node measurement. However, in excluding >10 % of patients who underwent "watch and wait," it cannot be universally applied to all patients. Found to be equally valid in predicting PFS for the majority (59 %) of patients treated with rituximab-containing regimens, it will be interesting to chart the discriminating power of FLIPI2 for OS with more prolonged follow-up. To date, two additional comparisons between the FLIPI and FLIPI2 performed suggest that the FLIPI score may be more discriminatory [11, 12].

Gene expression profiling and immunohistochemical analyses of the malignant cells and tumor microenvironment, using the immune-response signatures referred to as IR-1 and IR-2, are promising prognostic markers [13–18]. With discordant results, however, they are not yet sufficiently robust nor available to replace the traditional clinical indices used to assess patients' prognosis and decide the optimal therapeutic strategy. The most commonly used international criteria for starting cytotoxic therapy are listed in Table 9.2 [30]. These indices include bulky disease (either masses >7 cm or >3 nodal areas measuring 3 cm), local symptoms or compromised organ function due to tumor, B symptoms, elevated LDH or β_2-microglobulin, and cytopenias due to marrow involvement.

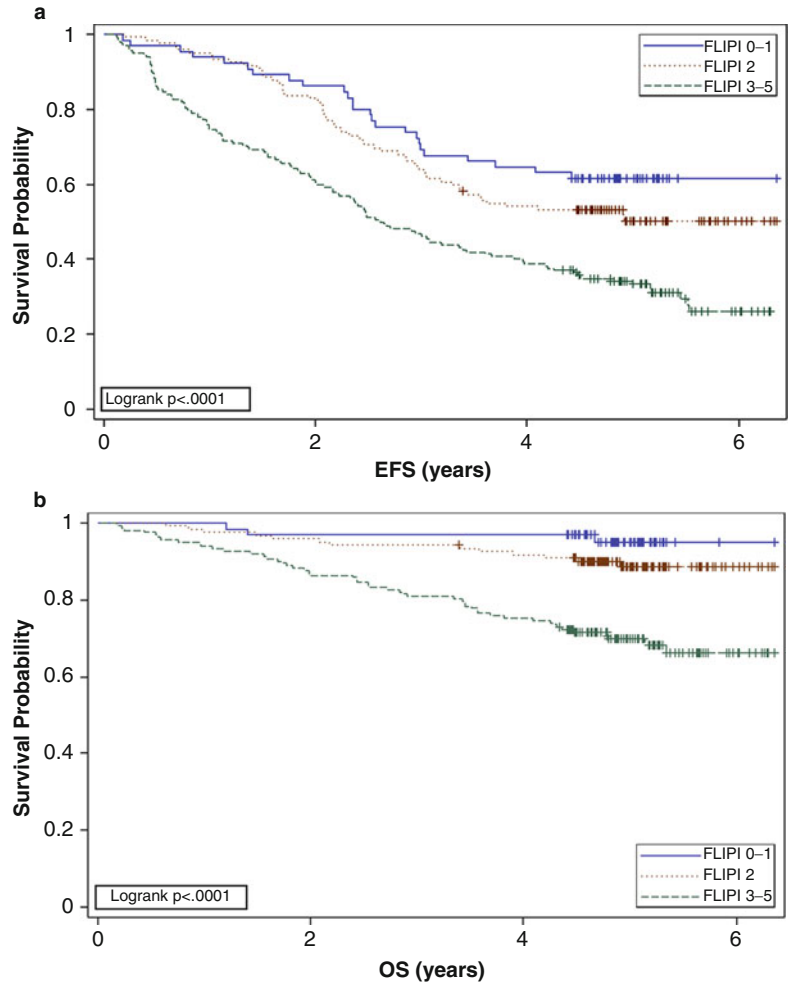

Fig. 9.1 Event-free survival (**a**) and overall survival (**b**) of patients receiving R-CHVP + interferon in the FL2000 study according to the FLIPI score

Table 9.2 Criteria for starting a cytotoxic treatment in follicular lymphoma patients

Adapted GELF criteria (FL2000 and PRIMA studies): any one of these criteria	BNLI criteria [30]: any one of these criteria
High tumor bulk defined by either: A tumor > 7 cm 3 nodes in 3 distinct areas each > 3 cm Symptomatic splenic enlargement Organ compression Ascites or pleural effusion	Rapid generalized disease progression in the preceding 3 months Life-threatening organ involvement Renal or macroscopic liver infiltration Bone lesions
Presence of systemic symptoms	Presence of systemic symptoms or pruritus
ECOG performance status > 1[a]	
Serum LDH or beta2-microglobulin above normal values	Hemoglobin < 10 g/dL or WBC < 3.0×10^9/L or platelet counts < 100×10^9/L, related to marrow involvement

[a]Used in the FL2000 but not in the PRIMA study, given the low percentage of patients with this sole criteria in the former studies (Salles G, personal communication 2012)

Table 9.3 Treatments used in newly diagnosed patients with follicular lymphoma (USA, 2004–2007) [27]

Treatment	Patients with all stages (n = 2,728) (%)	Patients with stage I (n = 474) (%)
Chemotherapy plus rituximab	51.9	30.4
Observation	17.7	28.7
Rituximab monotherapy	13.9	12.9
Radiation therapy	5.6	23.4
Clinical trial	6.1	–
Chemotherapy	3.2	2.5
Others	1.6	2.1

Initial Management of Early-Stage Disease

In the 10–15 % of patients with truly localized disease, the traditional treatment strategy had been radiation therapy (up to 36 Gy for bulky disease), given the radiosensitivity of FL, the prolonged OS in observational studies, and the alleged potential for cure [19, 20]. The FLIPI is of prognostic value in this patient group [21]. Despite the benefit of this strategy indicated in a large retrospective study [22] and published NCCN and ESMO guidelines [23, 24], the consensus on radiation therapy is not firm. Many clinicians adopt a watch and wait strategy [25], while others advocate combined modalities [26]. In a large prospective US cohort, radiotherapy was used as the sole treatment in only 23 % of patients with stage I disease and administered after chemotherapy in another 8 % [27] (Table 9.3). A systemic approach may indeed be appropriate for symptomatic patients with stage II disease when significant morbidity from radiotherapy could be expected based on tumor location. Prospective studies are lacking but there is merit in assessing whether a subset of high-risk patients with early-stage disease may benefit from a combined modality approach.

Advanced-Stage Disease: From Watch and Wait to Immunochemotherapy

Some Patients May Not Need Immediate Therapy

A period of observation has been a reasonable option for asymptomatic patients with low bulk disease to date. The median time to therapy with initial observation of asymptomatic patients was 2.6–3 years [28, 29]. Several retrospective and prospective studies demonstrate comparable overall survival using this approach compared

with initial chemotherapy treatment [25, 30, 31]. One study found no increased risk of histologic transformation [28], contrary to other reports [29, 32]. The rationale for observation is being challenged in an era of efficacious, minimally toxic immunotherapy such as rituximab. Furthermore, in this internet era, with broader patient understanding and participation in treatment decision making, given the absence of a survival detriment, many patients and their clinicians prefer the earlier introduction of therapy to the uncertainty of living with an untreated cancer. In a recent preliminary report of a Phase III study, rituximab monotherapy (4× weekly) followed by maintenance (every 2 months for 2 years) significantly improved the time to initiation of a new treatment and progression-free survival in patients with asymptomatic, non-bulky, advanced-stage disease when compared to watchful waiting [33]. Follow-up of this study is short and this outcome was anticipated, but both the "duration of rituximab benefit" (i.e., the potential impact of prior rituximab exposure on the response to first and second new treatments) and any overall survival difference have yet to be determined. Another caveat lies in the unknown long-term immune and infectious consequences of early and repeated rituximab exposure.

Options Available When Treatment Is Needed

Traditionally, therapeutic decision making for follicular lymphoma has been based on choosing between two goals: optimizing quality of life versus aiming for prolonged survival. However, rarely are patient priorities solely one or the other, but a relative balance of the two. Patient- and disease-related prognostic factors impact on the ability of the clinician to meet both priorities, after comprehensive discussion with the patient. Furthermore, patient priorities may change and clinicians need be mindful of the impact of first-line therapy on subsequent treatment options in this chronic "incurable" disease. The absence of consensus on the optimal first-line therapy for FL and the consequent plethora of individualized approaches are highlighted in a US prospective cohort study of patients treated between 2004 and 2007 [27] (Table 9.3).

Before the advent of monoclonal antibodies, several therapeutic approaches were studied. Institutional and epidemiologic data support improved outcomes, and important lessons can be learnt from this era [34–36]. In patients with symptomatic stage III–IV disease, past treatments included the combination of anthracycline with alkylating agents, interferon administration, the use of purine analogues, and high-dose therapy with autologous hematopoietic cell transplant. Although response duration was usually prolonged, leading to marginal survival improvements in subgroup analyses [36–39] until now, no approach has shown to be unequivocally superior with identified drawbacks to each. The significantly prolonged PFS after anthracycline use (most commonly in CHOP) incurs some additional morbidity and risk of cardiac toxicity without clear evidence of a reduction in risk of histologic transformation. The considerable morbidity from interferon despite its survival benefit has precluded common use of this agent, as has the stem cell toxicity and incidence of late infections after fludarabine. Likewise, while three studies demonstrate improved progression-free survival after autologous transplantation, the considerable morbidity, increased incidence of secondary neoplasia, and lack of overall survival benefit argue against its incorporation as a first-line consolidative approach [40–42].

It was also commonly believed that the initial treatment was unable to alter the ultimate prolonged course of this incurable disease, and therapies were used sequentially for disease progression. This classical paradigm has been strongly challenged with two observations. Firstly, it is now clear that overall survival can be improved by a combination of rituximab plus chemotherapy for patients needing therapy. Secondly, while most studies have been hampered by short-term follow-up, it is increasingly acknowledged that, even in this indolent histology, the depth of remission is correlated with both remission duration and prolonged overall survival. The very long-term follow-up (median 14.9 years) of patients in the GELF86 studies

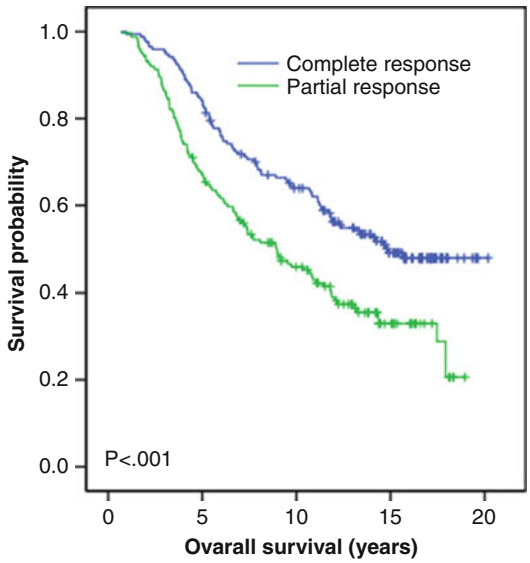

Fig. 9.2 Influence of response to first-line therapy in follicular lymphoma (excluding watch and wait patients) on overall survival ($p<.001$ in univariate and multivariate analysis)

recently demonstrated that patients achieving CR after first-line treatment had a significantly better OS than those reaching a PR (HR = 0.55, $p<0.001$) (Fig. 9.2) [43]. Furthermore, follicular lymphoma is universally [^{18F}]fluorodeoxyglucose (FDG) avid. A recent retrospective analysis demonstrated the markedly inferior outcome of a quarter of patients remaining PET positive after therapy with a significantly ($p<.0001$) inferior progression-free survival (PFS) at 42 months of 32.9 % compared to 70.7 % in those who became PET negative. The risk of death was also increased in PET-positive patients (hazard ratio 7.0; $p=.0011$) [44]. This data, if confirmed in prospective studies, strongly supports the benefit of achieving the best disease response in FL patients, but the definition of a true CR using PET will need to be clearly defined in this heterogeneously glucose avid histology.

First-Line Therapy with Rituximab Alone: As a Short Course or with Maintenance

Having decided that treatment is necessary, and where the principal priority is palliation of symptoms, there is a large body of literature using rituximab alone as a short course or with maintenance [45–48]. These studies mostly included patients with favorable disease characteristics (low tumor burden or low/intermediate FLIPI score). Such an approach is particularly relevant for elderly patients with multiple comorbidities and an otherwise shortened life expectancy. Approximately 75 % patients respond to 4 weekly doses of rituximab, with half of these responders achieving a complete response (CR). The median time to disease progression was reproducibly short: 18–24 months, but prolonged by maintenance rituximab. However, the "duration of rituximab benefit," defined as the time without need to start a cytotoxic regimen, was no different, suggesting rituximab retreatment at time of progression could be as effective as maintenance. Long-term follow-up of the ECOG 4402, RWW, and SAKK 35/03 studies will clarify this issue for these low tumor burden patients.

First-Line Therapy Combining Rituximab and Chemotherapy

Combination immunochemotherapy is appropriate when, most commonly, the treatment priority is to maximize depth of the response rate and progression-free and overall survival. There exists a plethora of therapeutic options often with attendant trade-offs between toxicity and depth of response. The addition of rituximab to conventional chemotherapy has demonstrated markedly improved response rates and progression-free and overall survival in several randomized studies (Table 9.4) [5, 8, 49–52]. The proportion of patients within each FLIPI score was similar, but control chemotherapy arms were different, hampering a straight comparison of these trials. A Phase III study of CVP chemotherapy with or without rituximab was performed in the first study [49]. Patients received consolidation with autologous stem cell transplant or interferon in the second study [50], or interferon alone in another [8], while in the final study (where patients also received interferon), the number of chemotherapy cycles was divided by 2 in the rituximab-containing arm [51] (Table 9.4). Sequential consolidation rituximab after chemotherapy was similarly shown to improve PFS in several studies [53–55].

Altogether, these studies demonstrate that first-line treatment combining rituximab with or after

Table 9.4 Randomized studies in follicular lymphoma patients using rituximab plus chemotherapy

Treatments	Patients within each FLIPI stratum (% with low/intermediate/high risk, respectively)	Median age (years)	Estimated PFS in the experimental arm	Progression-free survival (median)		Overall survival	
				Control arm	Experimental arm	Control arm	Experimental arm
CVP versus R-CVP [5, 49]	19/41/40	52	50 % (at 3 years)	15 months	34 months	77 % (at 4 years)	83 %[d] (at 4 years)
CHOP versus R-CHOP[a] [50, 52]	14/41/45	55	80 % (at 2 years)	31 months	Not reached	84 % (at 5 years)	90 %[d] (at 5 years)
MCP versus R-MCP[b] [8]	7/37/56	59	71 % (at 4 years)	26 months	Not reached	74 % (at 4 years)	87 %[d] (at 4 years)
CHVP+I versus R-CHVP+I[c] [51]	19/35/46	61	53 % (at 5 years)	35 months	Not reached	79 % (at 5 years)	84 % (at 5 years)

[a]CHOP or R-CHOP was followed by ASCT or IFN
[b]MCP and R-MCP were followed by IFN consolidation
[c]CHVP combined with interferon: 12 chemotherapy courses in the control arm versus 6 in the rituximab-containing arm
[d]*p* value for difference in overall survival significant

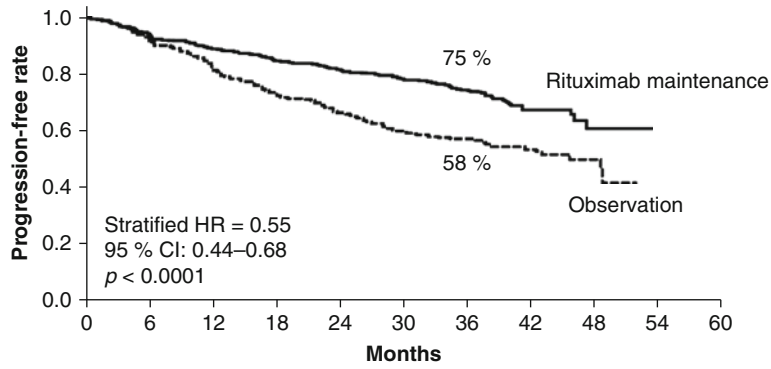

Fig. 9.3 Kaplan–Meier estimates of progression-free survival from randomization with rituximab maintenance versus observation

chemotherapy can improve outcomes. A meta-analysis (including studies for relapsing patients) estimated the benefit of this combination in terms of risk reduction (hazard ratio) for mortality to 0.63 (95 % confidence interval 0.51–0.79). The benefit in overall survival observed across the studies is noteworthy given that most patients not receiving rituximab as part of induction therapy likely received monoclonal antibodies at time of progression. Improved survival despite this crossover further endorses combined immunochemotherapy as a new standard in the first-line treatment of advanced follicular lymphoma.

Despite recent progress, the prognosis of the patient with high FLIPI remains unsatisfactory (median 5 year OS of 60 %) [51]. The preference for a first-line chemotherapy regimen containing or not an anthracycline remains debated, but when using R-CVP, median time to progression was only 26 months in one study [5]. Recent data, including a randomized study, indicate a significant improvement in progression-free survival with R-CHOP [56, 57]. Long-term follow-up of overall survival in randomized studies using anthracycline in the rituximab era may help to clarify this issue.

Maintenance Rituximab After Frontline Combination Therapy

Recently, the largest international study conducted in FL, the 1,200 patient PRIMA study, demonstrated the benefit of 2-year rituximab maintenance after first-line rituximab/chemotherapy [58]. Probability of achieving CR was significantly higher in patients receiving rituximab maintenance compared to those undergoing observation (72 vs. 52 %). After a median follow-up of 36 months, the PFS in patients receiving rituximab maintenance was 75 % compared to only 58 % in patients undergoing observation (hazard ratio 0.55; 95 % CI 0.44–0.68), Fig. 9.3. Maintenance therapy was well tolerated with Grade 3/4 adverse events occurring in 24 % compared to 17 % in the observation arm, and quality of life measures were comparable in both groups.

Frontline Therapy Using Radioimmunoconjugates, Alone or After Chemotherapy

Radioimmunoconjugates have also been studied in first-line treatment of follicular lymphoma, either as single agent or as consolidation therapy. Kaminski and colleagues reported the frontline use of ^{131}I-tositumomab in 76 patients [59] with a very high response rate (95 %) and 3 quarters of patients achieving CR. Toxicity was limited and the 5-year progression-free survival was 59 %. Although those patients were selected based on their limited marrow infiltration, these results are challenging in comparison with other trials including a substantial proportion of low tumor burden patients. Other studies demonstrated the potential of radioimmunotherapy to improve response rate and quality after either CHOP [60], fludarabine, [61] or rituximab followed by R-CHOP [62]. In the CHOP-^{131} I-tositumomab study, the estimated 5-year overall survival (OS) was 87 % and the progression-free survival (PFS) 67 % [60]. A large Phase III study [63] demonstrated a consistently high CR/CRu rate of 77 % with ^{90}Y-Ibritumomab tiuxetan used for remission consolidation after chemotherapy regardless of the initial chemotherapy used. Adjuvant ^{90}Y-ibritutomab also improved

progression-free survival ($p<0.0001$; HR 0.47) compared to observation. However, only a minority of patients in this study (13 %) received a rituximab-containing induction regimen [63]; hence, the role of radioimmunotherapy in the rituximab-chemotherapy era remains to be clarified. Prospective study of adjuvant radioimmunotherapy in patients failing to obtain CR may be of particular value. The current US intergroup trial is comparing R-CHOP versus CHOP followed by tositumomab. Despite its promise, access to radioimmunotherapy still remains limited internationally, and this will need to be addressed if the positive outcomes of clinical research are to be translated into the clinic.

Other Emerging Agents

Bendamustine, an agent with both alkylating agent and purine analogue properties, demonstrates excellent responses in patients refractory to rituximab and chemotherapy (ORR 77–92 % and CR 34–55 %) [64, 65]. Short-term toxicities are low, with an absence of alopecia or mucositis. A recently reported Phase III study compared first-line rituximab-bendamustine (90 mg/m^2 days1 + 2) with standard R-CHOP. Of 513 patients randomized, 54 % had follicular lymphoma. There was an improved tolerance in the R-bendamustine arm with a lower rate of neutropenia (11 % vs. 47 %, $p=0.0001$). There was a comparable 92 % overall response rate but notably an improved CR rate (39 vs. 30 %, $p=0.03$) and PFS (55 vs. 35 months, $p=0.00012$). While follow-up in this study is short (median 32 months) [66], and long-term toxicities remain unknown, this early data supports the possibility of using this agent first-line for follicular lymphoma patients. The validation of this data in other current trials is eagerly awaited.

Management of Patients in Second Line

Multiple options are available when the response to first-line therapy fails, and again it is not appropriate to define a "standard a care" to recommend for all patients. At diagnosis, the principal factors driving therapeutic decision making are patient age, fitness, and priorities. Additional important considerations are documentation of histological transformation (which would prompt strategies used in diffuse large B-cell lymphoma), the patient's tolerance of first-line therapy, and the depth and duration of previous response. Subsequent therapies include the ongoing observation of the asymptomatic patient with limited tumor bulk, the re-administration of single-agent rituximab, the use of multiple cytotoxic agents (alone, in combination, or with rituximab), as well as the use of autologous or allogeneic transplantation for remission consolidation. Multiple studies have been reported supporting the use of anthracycline when not incorporated in front line [67], fludarabine, [68–70] and bendamustine [65, 71–73], this last option being commonly used in recent years because of its favorable efficacy/toxicity ratio, including for patients failing previous rituximab-containing treatments. The few randomized studies available usually assessed the addition of another drug to a regimen commonly used, rather than comparing different strategies. For example, several studies have demonstrated the benefit of adding rituximab maintenance in patients responding to salvage therapy [67, 68] or the use of rituximab in the context of autologous transplant [74]. A recent trial indicated that bortezomib had little value when combined with rituximab [75].

The potential benefit of autologous stem cell transplantation as consolidation of second-line treatment is not firmly established [76]. Single center studies [77, 78] and retrospective cohorts [79] showed the efficacy of this approach, and one single randomized study, although underpowered, indicated a significant benefit in terms of event-free and overall survival [80]. Retrospective analyses of patients previously registered in first-line trials have also suggested a benefit of autologous transplant, even the rituximab era [81, 82]. Finally, in the European Bone Marrow Transplant study of rituximab for induction and maintenance in the context of autologous transplant [74], the median PFS after transplant exceeded 5 years in the rituximab-containing arms, a remarkable result generally not achieved with other strategies. For these reasons, many clinicians consider autologous transplant consolidation as a treatment of choice in eligible patients relapsing or progressing after first-line immunochemotherapy, particularly when the

disease tempo is rapid with an interval between first treatment and failure of only a few years. Allogeneic transplant approaches likewise lack prospective study, but registry data suggests allogeneic transplantation can be an effective therapy that may provide a plateau in progression-free survival curves [83]. Comparisons between autologous and allogeneic transplant from registry data demonstrate the predictably higher mortality (from infection and GVHD) over the first 5-year period with the latter approach, but a lower relapse rate thereafter [84]. Emerging single institution data also supports the role of reduced intensity conditioning in reducing this prohibitive mortality [85]. With the lure of a cure, allogeneic transplantation is an option that should be reserved only for very selected fit young patients with relapsed/resistant disease, usually after failure of autologous transplant.

Future Developments

New Agents in Follicular Lymphoma

There is encouraging preliminary phase II data on second-generation monoclonal antibodies, notably obinutuzumab (GA101) a fully humanized anti-CD20 [86], and on an immunomodulatory approach with combined rituximab and lenalidomide [87]. Other agents such as monoclonal antibodies directed against different antigens, drugs modulating apoptosis, or intracellular signaling are also worth investigating in FL patients, as long as they have a reasonable safety profile, given the prolonged life expectancy of these patients [88].

Current Risk-Adapted Therapeutic Strategies in Fl and Challenges for the Next Years

Since biologically derived prognostic factors are not yet available to identify patients with specific risks or deserving targeted therapeutic options, clinical criteria remain relevant for deciding on when to commence treatment for patients with FL (Table 9.2). These criteria, along with FLIPI 1/2 and patient individual priorities, assist clinicians in determining the appropriate first-line therapy for each patient. As an incurable disease, it remains important to consider the side effects and long-term risks of both first-line and subsequent therapies. Nonetheless, the development of highly efficient and tolerable strategies based around monoclonal antibody therapy has revised our therapeutic standards in FL. Combination immunochemotherapy strategies followed by maintenance rituximab aimed at durable complete remissions will likely lead to long-term survival improvement.

Finally, acknowledging the limitations of conventional CT response assessment, we need to better define remission status and our therapeutic goals. If prospective study of standardized post-therapy PET-CT response criteria confirms this imaging modality is highly predictive of both PFS and OS, then, as with other lymphomas, these criteria provide a meaningful clinical endpoint for study of response adapted strategies. The challenge will be in choosing from the plethora of promising consolidative therapies, beyond the now well-established program of maintenance rituximab to the study of alternative chemo- and antibody therapies, radioimmunoconjugates, and immunomodulatory agents, with or without autologous transplantation.

The near future promises to bring new standards of first-line therapy for follicular lymphoma. However, these are not likely to remain standard for long as, with each new research development prolonging survival, we may move closer to a cure.

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