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Diagnosis and treatment of follicular lymphoma

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Summary

Follicular lymphoma is a slow-growing disease exhibiting a heterogeneous clinical course, with a subset of patients experiencing a rapid disease course in the first two years and some developing disease transformation to a more aggressive phenotype. The advent of highly effective therapies has resulted in an increasing number of patients who achieve long-term progression-free survival alongside a good quality of life. Monoclonal antibodies, such as rituximab, either alone or in combination with chemotherapy regimens or radioimmunotherapy have been used with significant improvements in outcome. New treatment strategies such as new antibodies, biologic agents or vaccination therapy are also under investigation for the treatment of relapsed or refractory disease, further expanding the available options for patients and physicians alike. This article presents an overview of the current therapeutic strategies for the management of follicular lymphoma, focusing on the issues encountered in clinical practice.

Key words: *follicular lymphoma; first-line treatment; maintenance treatment; relapse/refractory disease; rituximab*

Introduction

Follicular lymphoma is the most commonly-occurring form of indolent lymphoma, and accounts for 20–25% of all lymphomas [1]. The majority of patients initially present with disseminated disease that follows a relatively indolent clinical course. Follicular lymphoma is characterised by response to treatment with disease-free or asymptomatic disease intervals, alternating with recurrence/progression and may transform to aggressive lymphoma at a rate of around 3% per year [2].

This article provides an overview of the current treatment strategy for follicular lymphoma. Given the large spectrum of available data, the aim of this review is to discuss some of the key issues which are encountered in clinical practice relating to first-line and maintenance therapy, and the treatment of relapsed/refractory follicular lymphoma.

Diagnosis and staging of follicular lymphoma

Complete staging of follicular lymphoma at diagnosis is an essential first step in making the appropriate therapeutic decision, to individualise therapy and to evaluate the patient response to treatment [3]. Most follicular lymphoma patients present with small- to medium-sized superficial lymph nodes which may have been neglected for prolonged periods of time [2]. The majority of follicular lymphoma cases are diagnosed through histological examination of such lymph nodes, with bone marrow involvement found in approximately 60% of patients [2]. At initial diagnosis, excisional lymph node biopsies of accessible lymph nodes should be analysed by a haematopathologist experienced in lymphoma diagnosis [4]. Fine-needle aspiration biopsies are not deemed appropriate for the initial diagnosis of follicular lymphoma [5]. In addition, initial tumour staging also involves the use of computed tomography (CT) scans, examination of bone marrow aspirates and biopsies by immunohistochemistry [5]. In cases of disseminated disease or large tumour bulk, positron emission tomography (PET) can be a useful tool to guide the choice of biopsy site [6]. However, routine use of PET is not yet recommended in patients with follicular lymphoma with the possible excep-

tion of confirming localised stage I/II disease [7]. Tumour staging is performed according to the Ann Arbor system [5].

Follicular lymphoma is thought to originate from germinal centre B cells and retains its characteristic gene expression profile [8]. Morphologically, follicular lymphoma is composed of clonally related centrocytes (small cells) and centroblasts (large cells), and is divided into three grades based on the number of large B cells present [8]. In grades 1 and 2, the proportion of small cells is predominant, whereas grade 3 features a greater proportion of large cells. In grade 3A, centrocytes are still present whereas grade 3B follicular lymphoma is composed entirely of large blastic cells (table 1) [9]. Differences in genetic characteristics and clinical behaviour suggest that grade 3A follicular lymphoma may be more indolent and related to grades 1 and 2, whereas grade 3B is often associated with poor outcomes and appears to be more closely related to diffuse large B-cell lymphoma (DLBCL) [10]. There is some controversy surrounding the clinical relevance and reproducibility of this grading system, with many experts arguing in favour of considering grades 1 and 2 follicular lymphoma (which share a similar indolent clinical behaviour and outcome of treatment) as a single disease entity, with a distinction only at grade 3, which is generally considered as an aggressive disease (in particular grade 3B) and usually treated with doxorubicin-containing regimens [11–13]. Histological assessment of the disease usually follows the World Health Organisation (WHO) guidelines [14–16] as a basis for lymphoma grading. The presence of a diffuse area of large blastic cells in a follicular lymphoma of any grade is equivalent to DLBCL and a separate diagnosis should be made [16–18].

Prognostic systems

The first prognostic system specific to follicular lymphoma was developed by the Italian Lymphoma Intergroup (ILI) in the late 1990s [19]. Currently, the Follicular Lymphoma International Prognostic Index (FLIPI) [20] is deemed to be more applicable across a range of clinical settings [21–25] and is still commonly used. Both systems were developed prior to the introduction of monoclonal antibody therapy, which has profoundly changed the treatment and outcome of follicular lymphoma [26]. Hence, the FLIPI-2 was recently developed, in a prospective series of patients needing treatment, using parameters which were not previously amenable to retrospective analysis, and may represent a promising new tool for the identification of follicular lymphoma patients with different risk profiles in the era of immunochemotherapy [27]. A detailed discussion of the prognostic parameters used for follicular lymphoma is beyond the scope of this review, but the reader can refer to a number of recent publications on this subject [28, 29]. The FLIPI and FLIPI-2 indexes are summarised in table 2.

Table 1: Follicular lymphoma grading according to the WHO classification (modified after Harris et al. [14]).

Grading	**Definition**
Grade 1–2 (low grade)	0–15 centroblasts per hpf*
1	0–5 centroblasts per hpf
2	6–15 centroblasts per hpf
Grade 3	>15 centroblasts per hpf
3A	Centrocytes present
3B	Solid sheets of centroblasts
Pattern	**Proportion follicular**
Follicular	>75%
Follicular and diffuse	25–75%
Focally follicular	<25%
Diffuse	0%**

* hpf = high power field of 0.159 mm^2

** Diffuse areas containing >15 centroblasts per hpf are reported as DLBCL with FL (grades 1 to 2, 3A, or 3B). Note that in small biopsies the absence of follicles may reflect a sampling error

Table 2: The FLIPI [25] and FLIPI-2 [31] prognostic indexes for FL.

FLIPI (retrospective analysis; pre-rituximab era)				**FLIPI-2 (prospective analysis; rituximab era)**			
5 factors	Age	<60 years	vs. ≥60 years	5 factors	Age	<60 years	vs.≥60 years
	Haemoglobin	≥12g/dL	vs. <12g/dL		Haemoglobin	≥12g/dL	vs. <12g/dL
	Serum LDH	≤ULN	vs. >ULN		Serum β-2 microglobulin	≤ULN	vs. >ULN
	Ann Arbor stage	I-II	vs. III-IV		Bone marrow involvement	absent	vs. present
	No. of nodal sites	≤4	vs. >4		Longest diameter of largest lymph node	≤6 cm	vs >6 cm

Risk group	**No. of factors**	**5–year OS**	**10–year OS**	**Relative risk**	**Risk group**	**No. of factors**	**3–year PFS**	**3–year OS**	**5–year PFS**
Good	0–1	91%	71%	1	Good	0	91%	99%	79%
Intermediate	2	78%	51%	2.3	Intermediate	1–2	69%	96%	51%
Poor	≥3	53%	36%	4.3	Poor	≥3	51%	84%	20%

Watch and wait

Despite initially presenting with advanced stage disease, most follicular lymphoma patients do not have symptoms and/or a high tumour burden requiring immediate treatment at the time of diagnosis, and in many cases the disease remains indolent for many years without therapy [30, 31]. For the past 30 years, lymphoma experts have debated how to manage patients with indolent lymphoma who have a low tumour burden and no symptoms [32]. Clinical trials addressing the issue of immediate chemotherapy versus watchful waiting in asymptomatic advanced follicular lymphoma have demonstrated no difference in overall survival (OS) [33]. A recent trial testing the benefits of immediate rituximab treatment versus waiting until disease progression prior to initiating treatment, may be critical for resolving these issues. Initial results from this trial showed that early treatment with rituximab significantly delays the need for new therapy but a more prolonged follow up will be needed to understand whether this approach may alter the natural history of the disease. So far no benefit has been shown for OS [34]. Preliminary results from a quality of life (QOL) analysis from this trial showed that patients who received treatment with rituximab had reduced anxiety and improved functional well-being [35]. At baseline, patient QOL scores were similar or superior to those of the general population (as assessed by the FACT-G questionnaire), with the exception of inferior emotional well-being. Although patients on watch and wait also reported improvements in some QOL parameters, the greatest improvements in emotional and functional well-being were observed in patients who received either rituximab maintenance or monotherapy [35].

Whether early treatment of follicular lymphoma results in a decreased risk of transformation is a matter of debate. The evidence for this is conflicting, with some studies showing no difference in the risk of transformation between patients treated at diagnosis compared to those who did not receive immediate treatment [33, 36, 37], and other studies showing the opposite result [38]. It is important to note that these comparisons were made using treatment regimens other than immunochemotherapy, thereby calling into question their relevance for today's clinical practice. Although most physicians would not hesitate to begin therapy in those patients with symptomatic or rapidly progressing disease, the challenge is how to identify the asymptomatic patients who may benefit from immediate treatment. Clinicians have to rely on disease parameters (i.e. extent of tumour burden, presence of B symptoms, bone marrow involvement) and patient characteristics (i.e. age, presence of co-morbid conditions) to guide them in making this decision. The prognostic value of FLIPI was confirmed in patients who had undergone immunochemotherapy but it only gives an approximate evaluation of the expected outcome. Novel biomarkers may soon become available for the prediction of the disease course in the single patient, thus allowing individualised therapeutic approaches. However, research on their use in the current era of immunochemotherapy is still in the exploratory stages [39].

First-line treatment

The decision to start first-line treatment depends not only on the stage but also on the symptoms of the disease [7]. The Swiss Group for Clinical Cancer Research (SAKK) has included patients in their trials if at least one of the following signs is present: B symptoms; symptomatic enlarged lymph nodes or spleen; steady, clinically significant progression of lymphadenopathy, splenomegaly or other follicular lymphoma lesions documented by a 50% increase in size over a period of at least 6 months; involvement of at least 3 nodal sites (>3 cm), bulky disease (>7 cm), haemoglobin <10g/dL, and platelets <100 x 10^9/L due to bone marrow infiltration or splenomegaly [40].

The treatment of newly-diagnosed follicular lymphoma is challenging, primarily because of the variability in disease course and response to treatment. At present, the choice of first-line therapy depends upon several factors: 1) clinical characteristics (age, tumour stage, nodal sites involved, Hb, LDH), 2) tumour physical characteristics, such as size and rate of growth, 3) patient characteristics, such as age and co-morbidities, 4) the goal of treatment (i.e., long lasting remission vs. palliation) [30, 32] and finally, 5) the anticipated side-effects which are closely linked to the kind of drug used and might include hair-loss, fatigue, risk of neutropenic fever and polyneuropathy, to name the most predominant. It is worthwhile noting that the FLIPI, currently used to predict the risk of treatment failure and to stratify patients in clinical trials, has never been validated as a tool for deciding when treatment is needed (patients with low risk FLIPI may be symptomatic and patients with high risk FLIPI may not necessarily need immediate treatment).

Radiation therapy

Clinically, 15–30% and pathologically, less than 10% of follicular lymphoma patients present with stage I or II disease. Involved-field radiation therapy (RT) has resulted in long-term control of the disease and a possible cure in a subset of patients [41, 42]. Clinical data have suggested that up to 40% of stage I and limited stage II patients may achieve a durable remission through the use of RT [41, 43] and that a reduction of the radiation field to involved nodes has no negative impact regarding progression-free survival (PFS) and OS [44]. These results are encouraging with respect to long-term disease control, a possible cure for this subset of patients and reduced long-term toxicity with smaller irradiated volumes. However, there is no standard protocol for radiotherapy since the field size of radiotherapy and the dose applied varied substantially in these trials. Not surprisingly, PFS was influenced by tumour size and Ann Arbor stage [41]. Advani et al. [45] demonstrated that, in stage I and II follicular lymphoma patients, over half of the subjects who did not receive any therapy remained untreated at a median of 6 or more years, and survival was comparable to that seen in studies using immediate treatment.

In stage III and IV patients with low disease burden, low doses (15–32 Gy) of total lymphoid irradiation have resulted in good response rates and remission times. Radiotherapy has been shown to confer lasting disease remission with relatively low toxicity [46]. However, despite the high

degree of radiosensitivity of indolent lymphomas, little data are available regarding the optimal treatment regimen including optimal dose and radiotherapy volume, as well as for comparing long-term outcomes of radiotherapy to immunochemotherapy regimens. Currently, radiotherapy is not the treatment of choice for newly-diagnosed follicular lymphoma patients [41, 47–49] with stage III/IV disease in most Swiss centres. However, it may be an option for selected patients, for example for those who do not qualify for systemic treatment (see below).

Immunochemotherapy

For the majority (~80%) of follicular lymphoma patients who present with advanced disease requiring therapy, the advent of monoclonal antibodies and their incorporation into follicular lymphoma treatment regimens has greatly improved survival and patient outcomes [50]. Rituximab (MabThera®/Rituxan®) is a chimaeric monoclonal anti-CD20 antibody that is currently used as a single agent and also in combination with standard chemotherapy regimens for the treatment of B-cell lymphoma, including follicular lymphoma.

Single agent rituximab has also been shown to result in high response rates and prolonged remission periods. An initial study of rituximab monotherapy in 49 newly-diagnosed patients with Stage II, III or IV follicular lymphoma revealed good response rates (73% at four weeks post-therapy). Interestingly, long-term follow-up data revealed that patients showing a molecular response to rituximab (BCL-2 negativity) experienced longer PFS (37 months, versus 12 months for BCL-2 positive patients) [51, 52]. The median PFS was 23.5 months overall, 28.6 months for responders, and 37 months for those showing molecular response. Results from a study by the SAKK have suggested that individual factors predictive of event-free survival (EFS) following single agent rituximab treatment include low disease bulk (<5 cm), Ann Arbor stage < IV, limited number of previous therapies, and prolonged rituximab treatment [40, 53, 54].

There is a large body of clinical evidence demonstrating the superiority of combining rituximab with nearly any chemotherapy regimen compared to the chemotherapy regimen alone [55–58], thus moving this regimen to the forefront of first-line therapies for follicular lymphoma. Currently, there is some discussion over which partner chemotherapy regimen is most suitable for use alongside rituximab. The number of rituximab applications usually corresponds to the number of chemotherapy cycles applied and ranges between four and eight [55, 58]. Encouraging results from an initial Phase II trial [59] triggered additional pivotal studies exploring the benefits of combining rituximab with standard chemotherapy regimens, including CHOP [57], CVP [58], FCM [55], MCP [56, 60] and bendamustine [61] (table 3). Amongst the anthracycline-based regimens, CHOP is the most widely-used [62–64], while the CVP regimen is more often applied to elderly patients requiring treatment [65]. Bendamustine is an alkylating agent approved in Switzerland for the treatment of chronic lymphocytic leukaemia (CLL), and bendamustine plus rituximab has also been shown to be at least as effective as CHOP plus rituximab as a first-line therapy in patients with indolent non-Hodgkin lymphoma (NHL) [66]. In fact, the R-bendamustine regimen was associated with a remarkable improvement of a median PFS of 54.8 months compared to 34.8 months with R-CHOP ($p = 0.0002$) [61]. The combination of rituximab with several other chemotherapy regimens such as MCP [56] and fludarabine [67] has also been studied, albeit to a lesser extent. Regardless of the chemotherapy regimen, the use of rituximab has resulted in enhanced OS, disease control (as assessed by PFS, EFS, time to progression [TTP], time to treatment failure [TTF]) and response rates, as evidenced by a recent meta-analysis evaluating immunochemotherapy versus chemotherapy alone [68]. An analysis of 1,943 NHL patients revealed a 0.65 pooled hazard ratio for death (95% confidence intervals [CI]: 0.54–0.78) in favour of immunochemotherapy. Similar findings were seen in the subgroup of 1,480 follicular lymphoma patients (hazard ratio 0.63; 95% CI: 0.51–0.79).

Maintenance therapy

Despite the improved outlook for follicular lymphoma patients using effective first-line therapies, most patients experience relapses which necessitates the use of other well-tolerated treatment strategies to extend the duration of remission. One approach for achieving this goal is maintenance therapy.

One agent that has been explored for use in maintenance therapy is interferon (IFN) alpha [69, 70]. Although there is evidence that interferon alpha improves PFS and possibly OS when given together with chemotherapy [71], a meta-analysis of data from the pre-rituximab era suggest that the addition of interferon-alpha as maintenance therapy

Table 3: Commonly used induction therapy regimens in FL.

Treatment	Treatment status	Summary of results	References
R-CHOP	First line patients	Improvements in TTF (p <0.001), remission rate (p = 0.011), response duration (p <0.001), time to next chemotherapy (p <0.001), and OS (p = 0.016), compared to CHOP alone	[53]
R-CVP	First line patients	Improvements in overall and complete response (p <0.0001), TTP (p <0.0001), and TTF (p <0.0001), compared to CVP alone	[54]
R-MCP	First line patients	Improvements in overall and complete response (p = 0.0009, p = 0.004, respectively), EFS (p = 0.0001), PFS (p <0.0001), and OS (p = 0.0278), compared to MCP alone	[56]
R-bendamustine	First line patients	Improvements in CR (p = 0.0323), PFS, EFS and TTNT (p = 0.0002) over R-CHOP. No differences in OS or overall response.	[57]
R-FCM	Relapsed/ refractory patients	Improvements in PFS (p = 0.0381), OS (p = 0.0030), and overall response (p = 0.01), compared to FCM alone	[51]

for follicular lymphoma improves progression-free survival while the benefit for OS is less evident [69, 70]. In a recent report, pooled data from different randomised studies of the German Low Grade Lymphoma Study Group suggest that IFN-maintenance prolongs remission duration also after rituximab-containing induction treatments [72]. Nevertheless, any benefits of maintenance therapy with interferon has to be balanced against its significant toxicity that has a major impact on the patient's quality of life [69, 70, 73].

Rituximab, on the other hand, has seen growing use in maintenance therapy regimens over the past years for several reasons. Firstly, it has a good tolerability profile with no significant long-term or cumulative toxic effects. Secondly, its long half-life enables the clinician to maintain drug exposure while minimising the number of drug infusions. Finally, the rituximab target (CD20) is usually still expressed on the surface of residual lymphoma cells, increasing the chances of successful re-treatment [74].

One of the earliest studies showing the clinical benefits of rituximab maintenance therapy in follicular lymphoma was a Phase III trial by Ghielmini *et al* [54]. In this trial run by the SAKK (35/98 trial), newly-diagnosed (treatment-naive) and previously-treated follicular lymphoma patients received rituximab induction consisting of four weekly doses (375 mg/m²). Non-progressing patients were randomised to either observation with no further treatment or prolonged rituximab administration (four rituximab infusions every two months). Long-term results showed that a substantial proportion of patients experienced long-term remission following prolonged rituximab exposure [40]. The median EFS was 24 months for the rituximab maintenance arm, compared to 13 months for the observation arm (p <0.001). In a multivariate Cox regression analysis, prolonged rituximab treatment was the only favourable prognostic factor (hazard ratio (HR) 0.59; 95% CI: 0.39 to 0.88; p = 0.009), suggesting that this maintenance regimen could be used regardless of previous treatment, disease stage or Fc receptor phenotype [40].

Since then, there has been a growing body of evidence demonstrating the clinical advantages of rituximab maintenance therapy following various induction regimens, including chemotherapy with or without rituximab [75–78].

The European Organisation for Research and Treatment of Cancer conducted one of the pivotal Phase III trials in patients with relapsed or refractory follicular lymphoma (EORTC; 20891 trial). The study demonstrated the benefits of rituximab maintenance every three months for two years following chemotherapy or immunochemotherapy [76]. Compared to observation alone, rituximab maintenance yielded significant improvements in PFS after CHOP (median 42.2 vs. 11.6 months; p <0.0001) and R-CHOP (median 51.8 vs. 23.0 months; p <0.0043). OS after the second randomisation was also significantly improved: 85% at 3 years versus 77% with observation (HR, 0.52; p <0.011). With a longer-term follow up, the superior PFS was confirmed but the improvement in OS no longer reached statistical significance. This was possibly due to the unbalanced use of rituximab in the post-protocol salvage treatment [77]. A similar prolongation of response duration with rituximab maintenance therapy in patients with relapsed and refractory follicular and mantle cell lymphoma after combined immunochemotherapy (rituximab, fludarabine, cyclophosphamide and mitoxantrone) was also shown in a Phase III trial run by the German Low Grade Lymphoma Study Group (GLSG) [55].

Based on the encouraging results in patients with relapsed and refractory follicular lymphoma, the Primary RItuximab and MAintenance (PRIMA) trial run by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) was designed to evaluate the effects of a two-year rituximab maintenance regimen every two months, compared to observation only, following various first-line immunochemotherapy regimens [79]. Interim results at 25 months post-randomisation indicated that rituximab maintenance conferred significant PFS benefits (Hazard ratio 0.50; 95% CI: 0.39–0.64), but no effect on OS was seen. An additional follow-up will allow evaluation of a possible effect on OS. According to the authors of the present review, rituximab induction followed by rituximab maintenance can be re-used when the relapse occurs later than 1.0–1.5 years after the end of the last rituximab maintenance therapy, although this needs to be validated in future studies. A summary of the Phase III studies with rituximab maintenance is provided in table 4.

Although the benefits of rituximab maintenance therapy are widely accepted, issues on the appropriate timing, dosing and duration remain to be clarified. The optimal duration of rituximab maintenance treatment is currently under investigation in the SAKK 35/03 trial, in which patients (who received rituximab induction consisting of four weekly doses) receive rituximab maintenance every two months for either eight months or for a maximum of five years, or until progression or unacceptable toxicity [80].

Table 4: Phase III studies with rituximab maintenance in FL patients.

Group/Study	Induction regimen	Treatment Setting	Patients	Rituximab maintenance	Total rituximab infusions	Results
SAKK 35/98 [44]	Rituximab	Any line	N = 202	4 infusions every 2 months	4	Median EFS 13 vs. 24 months (p <0.001)
ECOG 1496 [74]	CVP	First-line	N = 228	4 weekly infusions every 6 months for 2 years	16	Median PFS 1.3 vs. 4.3 years (p <0.0001)
PRIMA [80]	CHOP, CVP, FCM + rituximab	First-line	N = 1018	Infusion every 2 months for 2 years	12	PFS at 2 years 66 vs. 82 % (p <0.0001)
EORTC 20981 [76]	CHOP +/- rituximab	Relapsed/ resistant	N = 334	Infusion every 3 months for 2 years	8	Median PFS 1.3 vs. 3.7 years (p <0.001)
GLSG [128]	FCM + rituximab	Relapsed/ refractory	N = 81	4 weekly infusions 3 and 9 months after induction	8	Median response duration 26 months vs. not reached (p = 0.035)

Consolidation therapy

The goal of consolidation therapy is to rapidly improve the response to first-line therapy by attaining complete response (CR) from partial response (PR), and, where possible, by achieving a molecular response [81, 82]. By eliminating minimal residual disease, the hope is to minimise the risk of relapse. Two of the main consolidation strategies are myeloablative therapy prior to autologous stem cell transplantation (SCT) and radioimmunotherapy (RIT).

Autologous SCT

Consolidation regimens consisting of myeloablative treatment followed by SCT were frequently explored in follicular lymphoma patients before the advent of rituximab therapy [83]. Recently, SCT consolidation after induction with R-CHOP was tested in a cohort of follicular lymphoma patients undergoing first remission, resulting in a five-year PFS rate of 79% [84]. Results from another study suggested that greater improvements in PFS and OS could be attained in patients undergoing transplantation earlier in the course of disease [85]. Long-term follow-up data suggest that myeloablative therapy with autologous bone marrow transplantation confers prolonged freedom from recurrence, reaching a plateau at around 12 years. Nevertheless, the toxicity of this treatment regimen has called into question its practical relevance in the rituximab era. The use of SCT as a consolidation treatment is restricted to younger, fit patients who do not respond to first line treatment [86], excluding its application in the wider follicular lymphoma patient population including those >60 years of age [87].

Radioimmunotherapy

Radioimmunotherapy combines the specificity of a monoclonal antibody directed against a tumour antigen with a radioisotope that is delivered to tumour sites [88]. Clinical data is available for the Yttrium-90 (^{90}Y) – labelled murine antibody ibritumomab tiuxetan (Zevalin®) and the Iodine-131 (^{131}I) – labelled antibody tositumumab (Bexxar®). ^{90}Y ibritumomab tiuxetan has been studied in several Phase II trials and in one recently-completed Phase III trial, the First-line Indolent Trial (FIT) [89–93]. The results from the FIT study showed that after chemotherapy, consolidation treatment with ^{90}Y ibritumomab tiuxetan had beneficial effects on PFS. However, no significant effects were observed in the subset of patients who received immunochemotherapy as induction treatment [93], and only few patients (13%) in the FIT study received ^{90}Y ibritumomab tiuxetan after immunochemotherapy. Two Phase II studies suggest that this consolidation strategy can also be active in the setting of rituximab-based induction treatment [94, 95]. Currently, Zevalin® is registered in Switzerland for consolidation treatment of follicular lymphoma following induction therapy.

^{131}I tositumumab has also been evaluated as consolidation therapy following various induction regimens (reviewed in Gregory *et al*. [96]), and is only approved in the US for the treatment of relapsed/refractory indolent lymphoma. However, the use of radio-iodinated antibodies for treating B-cell lymphomas has met with some reluctance, particularly because of the potential for separation of the radioisotope and its subsequent accumulation in the thyroid. Nevertheless, promising results have been obtained with ^{131}I tositumumab in follicular lymphoma, with high response rates (95%) and up to 75% complete responders after first-line therapy [97]. It is important to note that the patient cohort in this study consisted of individuals with a favourable prognostic profile. ^{131}I tositumumab has also been successfully employed for myeloablation prior to re-infusion of autologous peripheral stem cells, achieving an overall response rate of 90% and an estimated two-year PFS rate of 81% [98]. More long-term clinical studies including data after immunochemotherapy are needed to gain a better understanding of how ^{131}I tositumumab and ^{90}Y ibritumomab tiuxetan can be properly incorporated into the mainstream treatment strategies for follicular lymphoma.

Treatment of relapsed / refractory follicular lymphoma

As conventional therapy for follicular lymphoma is not curative, virtually all patients will at least develop a progressive or recurrent disease. Since transformation to a higher grade histologic subtype is an integral part of the natural history of follicular lymphoma, a repeated biopsy is strongly recommended before initiating re-treatment of the relapsed disease. This is particularly true for patients presenting with clinical signs or symptoms suggesting transformation, including rapid progression of lymphadenopathy, infiltration of uncommon extranodal sites, development of B-symptoms, elevated serum lactate dehydrogenase, and/ or hypercalcaemia.

In general, the treatment options for relapsed or refractory disease are similar to those for first-line therapy [4]. Likewise, not all patients with progressive or relapsed disease will necessarily require immediate therapy and asymptomatic patients might be followed closely for development of symptomatic disease or rapid progression. For patients in need of treatment, there is no accepted standard therapy. Therefore, practice varies greatly within the wide range of available treatment options including re-challenge of the initial treatment regimen (including rituximab as single agent), use of a non-cross-resistant chemotherapy scheme (preferably within a clinical trial) with or without rituximab, RIT with radio-labelled antibodies, and high dose chemotherapy with autologous or allogeneic SCT. In addition, involved-field or extended-field radiotherapy alone or in combination with systemic therapy may be an option.

The choice of therapy is driven by factors similar to those used to guide initial treatment, namely the extent and aggressiveness of the tumour burden including its clinical features, the characteristics of the patient [30, 32], as well as the efficacy of prior treatment regimens [7]. Patients who have a response duration significantly less than the expected mean PFS for the initial treatment regimen may be considered eligible for more aggressive therapy, such as the use of autologous SCT. These factors, in combination with the therapeutic goals, form the basis for selecting a treatment regimen when facing relapsed/ refractory disease.

The clinical practice guidelines set by the European Society for Medical Oncology (ESMO) recommend the use of a non-cross resistant regimen (for example, the use of

fludarabine after CHOP therapy) for relapses occurring in <12 months [7]. For patients with a duration of remission >6 months, ESMO guidelines recommend the inclusion of rituximab. Due to the generally indolent nature of the disease and the time frames in which disease progression occurs, there is some degree of overlap when defining "relapsed" versus "refractory" disease with regards to previous therapy. For clinical decision-making, we consider a patient to be refractory if disease symptoms recur less than 6 months following the last treatment.

Immunochemotherapy

An important issue for patients who relapse after initial rituximab treatment is the actual efficacy of rituximab re-treatment. Whereas the superiority of combined immunochemotherapy over chemotherapy alone has clearly been demonstrated in a large randomised trial of relapsed and refractory follicular lymphoma patients who had *not* previously received anthracycline or rituximab [76], the role of rituximab re-treatment in patients who *had* previously been treated with a rituximab-containing regimen has been systematically addressed in only a few underpowered trials to date.

Taken together, the available clinical data suggest that the majority of patients can benefit from a rituximab-containing regimen in the event of relapsed disease. Therefore, for most patients with relapsed follicular lymphoma treatment (or re-treatment) with rituximab, either alone or in combination with chemotherapy, is used. For patients with a poor performance status, single agent rituximab may be preferable due to its relatively low toxicity profile, while patients with a good performance status may prefer combination therapy for its superior response rates despite greater toxicity and a lack of evidence in improving OS rates. The development of novel antibodies may provide additional treatment options in this clinical setting in the near future.

Radioimmunotherapy

Radioimmunotherapy is another therapeutic option in the relapsed setting. In addition to their roles in consolidation therapy, ^{131}I tositumumab, ^{90}Y ibritumomab tiuxetan (as discussed in the previous section) as well as ^{131}I rituximab have been explored for the treatment of relapsed follicular lymphoma. In a Phase III study of rituximab-naive patients who had recurrent disease following chemotherapy, ^{90}Y ibritumomab tiuxetan treatment resulted in statistically significant higher ORR and CR rates compared to rituximab as a single agent, although duration of response (14.2 vs. 12.1 months) and time to progression (11.2 vs. 10.1 months) were not significantly different [99]. A single-arm Phase II study in 54 patients with rituximab-refractory follicular lymphoma achieved ORR and CR rates of 74% and 15%, respectively, upon treatment with ^{90}Y ibritumomab tiuxetan [100]. Another Phase II study of ^{131}I tositumumab in 40 patients with progressive disease resulted in ORR and CR rates of 65% and 38%, respectively [101]. In a 10 year clinical experience study with 142 patients with indolent NHL (mainly consisting of follicular lymphoma patients), the treatment of relapsed or refractory patients with ^{131}I rituximab resulted in ORR and CR rates of 67% and 50%, and with median PFS and OS rates of 39 months and 87 months, respectively [102]. ^{131}I tositumumab is not approved in Europe at present.

Autologous and allogeneic SCT

The use of autologous or allogeneic SCT in follicular lymphoma remains controversial. The marked survival benefits conferred by other treatment regimens have shifted the clinical focus away from SCT as a treatment option. Regarding autologous transplantation, the high incidence of bone marrow involvement in advanced stage follicular lymphoma raises doubts regarding potential contamination of the stem cell product. In general, prospective data on the long-term clinical benefits of autologous SCT in the treatment of relapsed follicular lymphoma are lacking, and most of the data available from transplant studies were gathered in the pre-rituximab era. Thus far, the only prospective randomised trial in relapsed follicular lymphoma is the Conventional chemotherapy, Unpurged, Purged autograft (CUP) trial run by the European Bone Marrow Transplant (EBMT) Registry [103]. Results from this study that included only a limited number of patients show a PFS and OS advantage of high-dose therapy followed by autologous SCT over conventional chemotherapy. However, the first-line treatment used in this patient cohort did not include rituximab, and the role of autologous SCT has not yet been properly studied in the current immunotherapy era. An extensive retrospective analysis of 254 patients (<61 years of age) with relapsed follicular lymphoma was performed by the GELA, and showed that event-free survival was best (67%) in patients who received rituximab-containing salvage therapy and autologous SCT [104]. This trend was apparent but did not reach statistical significance in patients who had already received rituximab-containing salvage therapy. In a retrospective review, Rohatiner *et al.* demonstrated that autologous SCT may result in prolonged survival without progression in nearly half of the patients, with a greater benefit for patients intensified in second remission, compared to those intensified later in the course of the disease [85]. The EBMT reported long-term outcomes on 693 patients with relapsed follicular lymphoma undergoing autologous SCT. With a median follow-up of 10.3 years, the 10–year PFS and OS rates were 31% and 52%, respectively. At a median of 7 years, 9% of patients had developed a second malignancy [105]. More recently, a study evaluated the effects of *in vivo* purging with rituximab and rituximab maintenance therapy (every three months for two years) in patients with relapsed follicular lymphoma undergoing high-dose therapy with BEAM conditioning [106]. The five-year PFS in patients receiving rituximab purging and maintenance therapy was improved compared to those receiving no therapy (54.8% versus 37.6%; $p = 0.05$), suggesting that incorporating rituximab into *in vivo* purging alongside maintenance treatment regimens may improve the outcome of SCT patients. Finally, Phase II studies have tested the feasibility of including RIT with high-dose therapy plus SCT [107]. Toxicity appeared acceptable and a retrospective comparison suggested longer survival times with this approach rather than with total body irradiation-based autologous SCT.

The theoretical advantages of allogeneic SCT include the absence of tumour contamination in the stem cell harvest and a potential immunologic graft-versus-tumour effect. However, the use of allogeneic SCT is hampered by the high transplant-related mortality rates (as high as 40%) which makes this option only feasible in young and fit patients [108]. With the goal of reducing the toxicity of allogeneic transplantation, reduced-intensity conditioning regimens have increasingly been used and retrospective series or single centre experiences suggest promising results with this approach [109, 110]. However, prospective and multicentre trials are needed to confirm these results, and in general, the long-term benefits of allogeneic and autologous SCT need to be further assessed before these treatments can be integrated into widespread clinical practice. We suggest that patients with follicular lymphoma who are candidates for autologous or allogeneic SCT be referred for a formal transplantation evaluation at first relapse or when they do not respond to first-line immunochemotherapy. This is particularly true for patients who experience relapse within two years of first-line therapy or while still receiving rituximab maintenance therapy.

New agents

Although a large proportion of follicular lymphoma patients respond to immunochemotherapy, there is a group of patients with resistant/refractory disease for whom there is a need for new agents to overcome the poor prognosis. There are three main groups of novel therapeutic agents: i) other monoclonal antibodies (novel anti-CD20 antibodies such as ofatumumab [111] and GA 101 [112] or antibodies against targets other than CD20), ii) agents that target signal transduction pathways (e.g., proteasome inhibitors [113]; Bcl-2 and Bcl-6 inhibitors), and iii) agents that target the non-neoplastic cells of the tumour microenvironment (immunomodulatory drugs e.g., lenalidomide [114]). Upcoming phase III studies will demonstrate if targeted therapies can further improve follicular lymphoma treatment.

Patient follow-up

In a disease with a long, unpredictable clinical course such as follicular lymphoma, long-term follow-up is essential for monitoring disease status regardless of the success of a therapeutic regimen. In addition, long-term follow up could provide valuable information on the impact of a particular treatment programme upon the patient's responsiveness to future therapies [30].

There are no prospective, randomised trials comparing various follow-up schedules. ESMO guidelines recommend that follicular lymphoma patients undergo a medical history and physical examination every three months for two years, every four to six months for the following three years, and then twice a year [7]. Patient examinations should focus on the presence of tumour transformation or secondary malignancies, such as secondary leukaemia. Blood counts and routine biochemical testing including measurement of LDH levels are recommended every six months for the initial two years, but should be performed in cases where disease progression is suspected. In such cases, patients are strongly advised to undergo tumour restaging. When imaging results give rise to a suspicion of relapse, a biopsy should be performed to confirm the presence of relapsed disease. Histopathologic examination allows confirmation of transformation to more aggressive disease. The role of routine imaging in the longitudinal follow-up of asymptomatic patients after response assessment is uncertain.

Metabolic imaging techniques including 18–fluoro-deoxyglucose PET in combination with CT are currently being explored for tumour staging and in patient follow-ups [115]. Computed tomography scanning alone is suitable for pre-treatment staging of tumours, but is less specific for assessing tumour response after therapy [116–118]. Although CT scanning can be used to determine the size and location of tumours, it cannot be used to differentiate between viable tumours and scar tissue. PET can be used to distinguish between viable tumours and necrotic or fibrotic residual tissue masses following treatment [119, 120], but it is associated with a proportion of false-positive and false-negative findings. A recent analysis of 277 scans from a subset of 160 patients enrolled in a large phase III study of untreated follicular lymphoma (PRIMA study) was presented at the annual meeting of the ASH 2010, showing that PET-CT can be a helpful predictor of PFS and complements response evaluation after first line therapy [121]. Patients with PET negativity showed prolonged PFS whether in conventional CR or PR. The heterogeneous nature of follicular lymphoma highlights the need for large clinical studies evaluating the accuracy and specificity of new imaging techniques before they can be incorporated into routine patient follow-ups.

Conclusions

The availability of anti-CD20 monoclonal antibodies has led to significant improvements in the clinical outcome of follicular lymphoma patients. Previously, the median survival of follicular lymphoma patients from diagnosis was 10 years [122], but patient survival has been extended in the last decades [26, 50]. However, this improvement began before the widespread introduction of anti-CD20 monoclonal antibodies in clinical practice and is likely a result of the sequential application of effective new therapies and improved supportive care. At present, despite recent advances in our understanding of the biology of follicular lymphoma, the heterogeneity of this disease remains a confounding factor in the quest to alter its natural history. Although anti-CD20 monoclonal antibodies have revolutionised the treatment of follicular lymphoma, their optimal method of administration remains to be defined. A proportion of patients still do not respond to or become refractory to rituximab-containing therapy. New anti-CD20 monoclonal antibodies and a variety of targeted treatments are indeed under development and trials studying prognostic biomarkers are ongoing. Improved treatment strategies may therefore become available in the future. Nevertheless, the prolonged natural course of the disease will require long-term follow-up data on safety and efficacy for a proper evaluation of any novel therapeutic approaches [26].

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