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Review Article
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New Treatment Options in Advanced Stage Follicular Lymphoma

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Abstract

Follicular lymphoma is one of the most common non-Hodgkin's lymphomas with an expected survival of more than 20 years for the majority of patients. This impressive outcome has been achieved with the introduction of immunochemotherapy, as first line treatment with remissions lasting over 8 years, followed by other treatment options at first or subsequent relapse. However, certain groups of patients still have a poor prognosis. In recent years the efficacy of chemotherapy regimens has been augmented by new compounds selectively targeting the cell surface, intracellular pathways, and/or the microenvironment. Some of these are beginning to change the therapeutic landscape. This review summarizes prognostic factors in follicular lymphoma in order to identify patients with greatest medical need for these new treatment options and reviews recent data from prospective clinical studies testing new agents in first-line and relapsed follicular lymphoma. Finally, we assess the current role of immunochemotherapy and discuss the requirements for future clinical trials.

Introduction

The overall prognosis of patients with follicular lymphoma (FL) has substantially improved over the last decades. With the introduction of the aggressive chemotherapies or purine analogs at the end of the seventies the median overall survival (OS) for all patients with low-grade FL (grade I/II) reached 18.5 years, and there was further improvement after the introduction of rituximab.[1] Using immunochemotherapy for advanced stage symptomatic patients FL is now a relapsing and remitting disease with a 5-year OS of more than 90% for the majority of patients.[2] However, certain subgroups of patients still have worse outcome and patients diagnosed in their forties and fifties will still have their life expectancy shortened by this disease.

With the expanding knowledge of the biology and pathogenesis of B cell malignancies, several new compounds acting through a variety of mechanisms have been investigated in FL. In contrast to cytostatic agents these agents are characterized by a specific target on the surface of the lymphoma cell, in the intracellular pathway or in the microenvironment of the lymphoma cell (with a selection of new compounds listed in Tables 1–3). Ideally, such new approaches should

- offer innovative options for high-risk patients,
- have the potential to overcome disease resistance that develops over time,
- avoid cumulative toxicities from successive therapies,
- reduce the risk of transformation and should raise the prospect of cure.

Currently, a plethora of new compounds with assumed activity in FL are tested in clinical trials. Therefore, the selection of drugs discussed in the review is somewhat subjective. The authors tried to focus on compounds which are more advanced in the clinical development or which may be prototypic for a group of compounds.

Prognostic factors

There are a number of factors that may influence the prognosis of patients with FL:

- The "Groupe d'Etude des Lymphomes Folliculaires" (GELF) and also the "National Comprehensive Cancer Network" (NCCN) defined clinical criteria to identify patients with advanced FL requiring therapy.[3,4]

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- The follicular lymphoma international prognostic index (FLIPI) and the updated FLIPI-2 summarize clinical and patient factors.[5,6] Based on these criteria, 3 different risk groups were identified, the so called high risk group, intermediate risk group, and low risk group. The FLIPI helps to estimate prognosis but does not play a role in the selection of therapy. Recently, a simplified but equally predictive index, the PRIMA-PI, was published and validated in population-based studies.[7,8] This prognostic tool comprises only 2 parameters: bone marrow involvement (yes/no) and β-2 microglobuline (>3 mg/L or ≤3 gm/L), defining 3 different risk categories.
- The combination of gene mutations and clinical factors has been described in the m7-FLIPI.[9] In particular, this model included the mutation status of seven genes (EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, and CARD11), the FLIPI, and the Eastern Cooperative Oncology Group performance status. Using this clinicogenetic risk model, a more precise prediction of prognosis is now possible. The m7-FLIPI allows the identification of a high-risk group with a very poor outcome. However, the mutational data of the m7-FLIPI are not yet routinely available in clinical practice nor has it been validated with newer therapies.
- There is also increasing understanding of the relevance of immune cells surrounding FL. In 2004, in a landmark paper Dave et al[10] described the molecular features of tumor-infiltrating immune cells which may predict survival of patients with FL. The authors identified gene-expression signatures correlating with good prognosis (called immune-response 1) and gene-expression signatures correlating with unfavorable diagnosis (called immune-response 2). Recently, a prognostically predictive 23-gene expression panel comprising genes both expressed in the microenvironment as well as those expressed in tumor cells demonstrated the role of both in determining outlook in FL.[11] Of note, the adverse prognostic value of the previously described "immune response 2" signature was not confirmed in this study.
- More recently, the role of the microenvironment has become increasingly recognized as not only influencing prognosis but also offering potential therapeutic targets.[12]
- Overall prognosis is greatly influenced by duration of first response. The National LymphoCare Study identified a group of 19% of patients who had early progression 2 years or less after initial immunochemotherapy (POD24 patients).[2] Five-year OS was 50% in the POD24 group compared to 90% in patients without early relapse. In a detailed analysis the following risk factors were associated with increased risk of progression or death before 24 months: male gender, ECOG ≥2, high-risk FLIPI score, or baseline β-2 microglobuline ≥3 mg/L.[13] Factors associated with favorable outcome were achieving a complete response (CR) and exposure to rituximab and/or anthracyclines.
- Based on a subgroup analysis of recent clinical trials there is also now a growing understanding of the prognostic value of positron emission tomography (PET).[14] For example, in the Gallium trial that evaluated the role of obinutuzumab in front-line FL, PET at the end of induction shows clear correlation with progression-free survival (PFS) and OS.[15,16]
- Minimal residual disease (MRD)-negativity at end of induction may also be a prognostic factor, this will be discussed later.

In summary, the prognosis of patients with FL depends on a variety of factors outline above. However, the decision to treat in most centers is still based on histological grading, clinical staging, concurrent symptoms, and tumor burden.

Immunochemotherapy

For patients with a low tumor burden, watchful waiting is still appropriate for those patients with asymptomatic disease since there is little evidence that early intervention in the asymptomatic patient has any effect on overall survival or risk of transformation.[17] This was also shown in a large prospective trial including 1754 stage II–IV patients who were managed by watchful waiting, rituximab monotherapy, or immunochemotherapy.[18] There was an improvement in the time to next therapy (TTNT) and the PFS with immunochemotherapy, and time to chemotherapy was improved with the use of rituximab. However, there was no effect on OS between all 3 treatment arms. It should be mentioned that the use of rituximab monotherapy may be an option for symptomatic patients with low tumor burden.

In patients requiring therapy, rituximab-based regimens such as R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), R-FC(M) (rituximab, fludarabine, cyclophosphamide, mitoxantrone), and rituximab plus bendamustine (BR) have become standard of care in most centers as first line treatment. In a randomized trial conducted by the Fondazione Italiana Linfomi R-CHOP and R-FM were superior to R-CVP in terms of eight-year PFS but with no significant differences in OS.[19,20] In addition, R-CHOP had a better risk-benefit ratio compared with R-FM. It has been also shown by others that fludarabine-containing regimens increase the risk of myelosuppression and infection[21] and consequently have fallen out of favor.

The STiL NHL 1-2003 trial compared R-CHOP with BR in a prospective, randomized study.[22] Here BR showed a significant better PFS compared to R-CHOP and was less toxic. The 10-year update was recently presented, which confirms a significant improvement regarding the time to next treatment for BR,[23] although no difference in overall survival was observed. Based on this trial, BR has become the standard first-line approach in many countries for symptomatic advanced stage FL.

There is still ongoing discussion on the role of maintenance in FL. In the prospective, randomized PRIMA trial, patients received rituximab maintenance versus observation following initial therapy with R-CHOP, R-CVP, or R-FCM.[24] There was a significant better PFS with rituximab maintenance compared to observation. At 10 years, 51% of the patients in the rituximab-maintenance arm versus 35% in the observation arm were free of disease progression.[25] Furthermore, median TTNT after 10 years was 6.6 years in the observation arm but has still not been reached in the maintenance arm, raising the possibility that some patients might be cured with immunochemotherapy plus maintenance. However, there was no effect on OS. These results were confirmed by a further study.[26] The efficacy of rituximab maintenance following initial treatment with BR has also been suggested,[27,28] but new safety signals (see below) and the absence of any impact on OS raise concerns about the value of maintenance in FL. The uncertainty of the long-term benefit of rituximab maintenance following rituximab-containing induction therapy was also discussed in a recent meta-analysis.[29]

Stem cell transplantation and CAR T cell therapy

For relapsed patients, the role and timing of auto- or allogeneic transplantation remains controversial. In 2013, the European Society for Blood and Marrow Transplantation (EBMT)

published a consensus project summarizing indication for hematopoietic stem cell transplantation in patients with FL.[30] They recommended autologous transplantation in high-risk first relapse or at the time of second relapse. In a retrospective analysis, the role of autologous transplantation was evaluated in POD24 patients, showing a significant improvement in the PFS and OS for high-dose compared to conventional therapy.[31] In a further retrospective analysis, improved OS was demonstrated in patients receiving autologous transplantation within 1 year of treatment failure.[32] However, another report suggested that autologous transplantation improved OS only in patients with histological transformation at the time of progression.[33]

Allogeneic transplantation should be considered at relapse after autologous transplantation. In a recent analysis of the EBMT data and the data of the Center for International Blood and Marrow Transplant Research (CIBMTR), the 3-year OS following allogeneic transplantation was 66%; however, the transplant-related mortality remains high at 25% at 3 years.[34] High-dose chemotherapy followed by autologous transplantation can be recommended for POD24 patients responding to second line therapy. The role of allogeneic transplantation, given the early mortality now needs to be reevaluated in the light of newer treatment options.

Chimeric antigen receptor (CAR) T cell therapy is a promising new class of cellular immunotherapy showing activity in several hematologic malignancies. These T cells are genetically modified to express CARs which recognize specific tumor targets and inducing an immune response leading to partial or complete tumor eradication.[35] T cells expressing CARs targeting the B cell antigen CD19 showed activity against acute lymphoblastic leukemia and relapsed B cell lymphoma. In a recent trial involving 28 adult patients with relapsed or refractory lymphoma, 10 out of 14 with FL who received autologous CAR T cells achieved a CR, and at a median follow-up of 28.6 months, 89% of these maintained the response.[36] In the entire cohort, 18% of patients developed a severe cytokine-release syndrome, and 11% developed serious encephalopathy. These data demonstrate the efficacy of CAR T cell therapy, but also highlight the risk of severe side effects associated with this approach.

Radioimmunotherapy (^{90}yttrium-ibritumomab-tiuxetan) may also represent an effective therapeutic approach in elderly patients with comorbidities not appropriate for transplantation.[37]

New targets and compounds

Targeting the cell surface

This group consists of monoclonal and bispecific antibodies and antibody drug conjugates. Beside rituximab the only antibody which has already been approved in the US and Europe for use in FL is obinutuzumab. This compound is a type II CD20 antibody with greater antibody-dependent cytotoxicity and direct apoptosis compared to rituximab.[38,39] In the GAUSS-trial, the direct comparison between rituximab and obinutuzumab did not show any difference for PFS between the 2 drugs given as single agents in relapsed FL.[40] In the GALLIUM trial in patients with untreated FL, obinutuzumab was combined with chemotherapy (CHOP, bendamustine, or CVP) and compared in a randomized study to rituximab plus chemotherapy, followed by maintenance in both arms.[41] In this study in 1202 patients, the estimated 3-year rate of progression-free survival was 80% for obinutuzumab and 73,3% for rituximab (HR (95% CI), 0.66 (0.51, 0.85; $P=0.0012$)). At present, there is no difference in the OS, but obinutuzumab offers delays to first relapse, thereby reducing the number of POD24 patients by 34%.[42] In further subgroup analysis, patients treated with obinutuzumab had a significant higher level of MRD—negativity at the end of induction compared to those treated with rituximab.[43] MRD response may also identify new prognostic risk groups which should be evaluated further. Based on these results, obinutuzumab has been approved for first-line treatment in combination with chemotherapy.

Patients receiving obinutuzumab had a higher number of grade 3 to 5 adverse events with a higher incidence of infusion-related reactions. Furthermore, bendamustine in both arms was associated with higher rates of grade 3 to 5 infection and second malignancies during the maintenance phase. This observation may be based on the T cell suppression by bendamustine, which has been reported also by other investigators and raised possible concerns about the use of bendamustine in frontline therapy. All users should be aware of potential side effects and also consider antiinfectious prophylaxis with cotrimoxazole.

In the randomized GADOLIN trial, obinutuzumab plus bendamustine was compared with bendamustine alone in relapsed patients who were refractory to rituximab.[44] The use of obinutuzumab and bendamustine significantly improved PFS and also OS and clearly demonstrate that obinutuzumab is also active in rituximab-refractory patients.

What can we learn from GAUSS, GALLIUM, and GADOLIN in terms of CD20 antibodies? Obinutuzumab plus chemotherapy is more effective than rituximab plus chemotherapy in frontline FL and represents a possible new standard of care. It is also effective in rituximab refractory patients. Longer follow up is required to establish its possible impact on long-term survival and the true incidence of second malignancies.

Blinatumomab is a CD19/CD3 BiTE (bispecific T-cell engager) antibody construct which was used in a phase I trial in different lymphoma subtypes.[45] In 15 patients with relapsed or refractory FL, the overall response rate (ORR) was 80%, and 6 patients had a response of more than 600 days. Neurologic events were dose limiting. Further trials with this promising compound are ongoing.

Table 1 lists a selection of investigational drugs targeting the cell surface.

Targeting intracellular pathways and epigenetic targets

This is an important group of compounds, consisting of phosphoinositide 3-kinase (PI3K)-inhibitors, Bruton's tyrosine kinase (BTK)-inhibitors, or BCL-2-inhibitors, which all are frequently used in several lymphoma subtypes. The only agent which is currently approved in multiply relapsed FL in Europe is the PI3K-Inhibitor idelalisib. Idelalisib is a highly selective oral bioavailable inhibitor of the δ isoform of the PI3K. Approval was based on a phase II study, which showed am median PFS of 11 months and a median OS of 20.3 months in 125 patients with indolent lymphomas refractory to both alkylators and rituximab, 72 of them with FL.[46] In a subgroup analysis, idelalisib also showed antitumor activity in patients high-risk FL relapsing within 24 months after initial immunochemotherapy.[47] A total of 22/37 (59,4%) patients achieved a ≥50% decrease in the lymphoma mass. The median PFS was 11.1 months with no significant differences between "early-early" relapse patients (progressing in ≤12 months) and "late-early" relapse patients

Table 1

Selected Investigational Drugs in Follicular Lymphoma: Targeting the Cell Surface

Agent	Target	Clinical Study	N	Response	Durability	Refs.
Frontline						
Epratuzumab	CD22	Phase II + rituximab	59	ORR 88%, CR 42%	3-y PFS 60%	Grant et al[67]
Galiximab	CD80	Phase II + rituximab	61	ORR 72%, CR 48%	4.3-y PFS, 2.9 y	Czuczman et al[68]
Relapse/refractory						
Ofatumumab	CD20	Phase II	116	ORR 11%	Median PFS 6 mo	Czuczman et al[69]
Polatuzumab Vedotin[a]	CD79b	Phase II + rituximab	45	ORR 73%, CR 33%	1-y PFS 63%	Advani et al[70]
^{177}Lu-Lilotomab Satetraxetan[b]	CD37	Phase I/II	21	ORR 81%, CR 28%	Median DOR 15 mo	Kolstad et al[71]
Blinatumumab	CD3/CD19	Phase II	15	ORR 80%, CR 40%	>20 mo PFS 40%	Goebeler et al[45]

CR = complete remission, DOR = duration of response, ORR = overall response rate, PFS = progression-free survival.

[a] Antibody drug conjugate.

[b] Antibody radionuclide conjugate.

(progressing 12–24 months). These data clearly demonstrate the activity of idelalisib in FL; however, investigators need to be aware of the effects. The most common adverse events reported were fatigue, diarrhea, nausea, rash, chills, and pyrexia, whereas the most frequent grade 3 and grade 4 adverse events were diarrhea, pneumonitis, and elevation of liver enzymes.[48] Reports of deaths because of opportunistic infections with *Pneumocystis jirovecii* and CMV reactivation halted phase III studies with idelalisib.[48] but further studies with appropriate prophylaxis may still be appropriate to evaluate the possible role of this agent or similar PI3K.

There are further PI3K-inhibitors that have been tested in phase II trials. Duvelisib, orally available, blocks the δ and γ isoforms of the PI3K. In the DYNAMO-trial, 83 patients with FL refractory to chemotherapy and rituximab achieved an ORR of 41%.[49] The median PFS was 8,3 months and the median OS was 11,1 months. Duvelisib had a manageable safety profile. Most common grade III/IV adverse events were transient cytopenias and diarrhea.

Copanlisib is an intravenously available PI3K inhibitor blocking the α and δ isoforms of the PI3K. In a phase II study of 142 patients (104 with FL), copanlisib showed an ORR of 59% with 14% CR.[50] The median PFS was 11.2 months, the median OS has not yet been reached. Most frequent adverse events were transient hyperglycemia and hypertension.[51] Copanlisib has less severe toxicities compared to idelalisib, and recently received FDA approval for relapsed FL.

INCB050465 is PI3Kδ inhibitor tested in a phase I/II study in relapsed or refractory B cell malignancies.[52] Interestingly, in this study toxicity was significantly reduced after an intermittent dosing schedule was implemented. Intermittent dosing of PI3K inhibitors, which are the most effective group of targeted drugs in FL to date, and whether combination therapy is superior to single agent therapy need be explored in future trials.

Ibrutinib is an orally available BTK-Inhibitor with high activity especially in chronic lymphocytic leukemia and mantle cell lymphoma. In a phase II trial, 60 patients with untreated FL were treated with a combination with rituximab.[53] The ORR was 85% with a CR rate of 35%. The PFS and OS after 2 years was 87% and 98%. The combination was well tolerated. In the DAWN trial, ibrutinib was used as single agent in relapsed FL refractory to chemotherapy.[54] A total of 110 patients had a median of 3 previous therapies. The ORR was 20.9% (CR 11%), with a median PFS of 4.6 months, and a 30-month OS of 61%. In a very recently published trial of 40 patients with recurrent FL, single agent ibrutinib achieved an ORR of 37.5%, with a median PFS of 14 months.[55]

Venetoclax inhibits BCL-2, normally overexpressed in FL. In a phase I trial, venetoclax was tested as single agent in various relapsed non-Hodgkin lymphomas.[56] In 29 patients with FL, the ORR was 38% (14% CR) with a median PFS of 11 months. Major toxicities were anemia, neutropenia, and fatigue.

In conclusion, current data with single agent ibrutinib or single agent venetoclax have modest activity in relapsed disease. Both agents will need combination partners to increase efficacy, and such studies are now underway.

Tazemetostat is an orally available inhibitor of the histone methyltransferase EZH2 which was used in a phase II trial in relapsed diffuse large B cell lymphoma and FL.[57] In FL, 28 patients with mutated EZH2 had an ORR of 71% (CR: 11%), and 54 patients with EZH2 wildtype had an ORR of 33% (CR: 6%) with some durable responses. The compound was well tolerated. These are promising but preliminary results especially for FL with activating EZH2 mutations.

Table 2 summarizes a selection of these investigational drugs with intracellular targets.

Targeting the microenvironment

In recent years there is an increasing understanding on the significance of the microenvironment on lymphoma growth and survival (see above).[11] Several compounds directly or indirectly interact with immune cells, blood vessels, or the extracellular matrix surrounding the lymphoma. Lenalidomide is a well-known immunomodulatory agent successfully used in multiple myeloma and various lymphoma subtypes, including mantle cell lymphoma. In FL, lenalidomide shows only limited activity as single agent but demonstrates promising results in combination with rituximab.[58] In a phase II trial of 50 untreated patients with FL, lenalidomide plus rituximab (R^2) achieved a CR rate of 87% and a 3-year PFS of 78.5%.[59] Major toxicity ≥grade 3 was neutropenia in 35% of patients. A total of 28% of patients required dose reductions. Overall, these results are comparable with data achieved with immunochemotherapy. Consequently, the phase III RELEVANCE trial directly compared R^2 with immunochemotherapy (R-CHOP, R-bendamustine, or R-CVP).[60,61] Final results showed no superiority of R^2 compared to standard treatment in the primary endpoints CR at 120 weeks and PFS at 30 months. Toxicity profiles for R^2 versus R-chemo differed, with higher grade III/IV neutropenia (32% versus 50%) with R-chemo, and higher grade III/IV cutaneous events (7% vs 1%) with R^2. Although this trial failed the primary endpoints, the study is of interest since it suggests equivalence between immunochemotherapy and a nonchemother-

Table 2

Selected Investigational Drugs in Follicular Lymphoma: Intracellular Targets

Agent	Target	Clinical Study	N	Response	Durability	Refs.
PI3K-inhibitors						
Duvelisib	PI3Kδγ	Phase II, R/R	83	ORR 41%	Median PFS 8.3 mo	Zinzani et al[49]
Copanlisib	PI3Kαδ	Phase II, R/R	104	ORR 59%, CR 14%	Median PFS 11.2 mo	Dreyling et al[50]
Umbralisib	PI3Kδ, casein kinase-1ε	Phase I, R/R	17	ORR 53%, CR 12%	Median PFS 16 mo	Burris et al[72]
BTK-inhibitors						
Ibrutinib	BTK	Phase II, frontline, +rituximab	60	ORR 85%, CR 35%	2-y PFS 87%	Fowler et al[53]
		Phase II, R/R	110	ORR 21%, CR 11%	Median PFS 4.6 mo	Gopal et al[54]
Acalabrutinib	BTK	Phase Ib, R/R	12	ORR 33%	Not reached	Fowler et al[73]
Other inhibitors						
Venetoclax	BCL-2	Phase I, R/R	29	ORR 38%, CR 14%	Median PFS 11 mo	Davids et al[56]
Entospletinib	Syk	Phase II, R/R	41	ORR 13%	Median PFS 5.5 mo	Sharman et al[74]
Vorinostat	HDAC	Phase II, frontline (n = 5) + R/R, +rituximab	22	ORR 50%, CR 41%	2-y PFS 61%	Chen et al[75]
Bortezomib	Proteasome	Phase II, R/R, +rituximab	45	ORR 64%	5-y PFS 34%	Bari et al[76]
Temsirolimus	MTOR	Phase II, R/R	39	ORR 54%, CR 26%	Median PFS 12.7 mo	Smith et al[77]
Tazemetostat	EZH2	Phase II, R/R	82	Mutated (n = 28): ORR 71% Wildtype (n = 54): ORR 33%	Mutated: median PFS > 49 wk Wildtype: median PFS > 30 wk	Morschhauser et al[57]

BCL = B-cell lymphoma, BTK = Bruton's tyrosine kinase, CR = complete remission, EZH = enhancer of Zeste homolog, HDAC = histone deacetylase, MTOR = mammalian target of rapamycin, ORR = overall response rate, PFS = progression-free survival, PI3K = phosphoinositide 3-kinase, R/R = relapsed/refractory, Syk = spleen tyrosine kinase.

apy approach. More subgroup analysis and longer follow-up is needed to draw final conclusions from this trial. In the relapsed setting, the MAGNIFY trial used R^2 in relapsed and refractory FL. The ORR of 117 patients was 67%, with 36% CR.[62] Interestingly, patients who were double refractory to both rituximab and alkylating agents achieved an ORR of 46% (CR, 21%). POD24 patients had also an ORR of 49% (CR, 12%). PFS after 1 year was comparable for patients with less than 2 lines of previous therapies compared to patients with 2 or more lines of prior therapies.[63] These data also demonstrate the efficacy of R^2 in high-risk relapsed patients and could be an important treatment option for patients not suitable for transplantation.

Currently, there is a major interest in the role of immune checkpoint inhibitors, so called blocker of the programmed cell death protein 1 (PD-1). These include nivolumab, pidilizumab, and pembrolizumab. Compared with other lymphoma subtypes, data for FL are scanty and very preliminary. While the anti-PD1 appear to have modest activity as single agent in patients with follicular lymphoma, in 15 rituximab-sensitive patients with relapsed FL treated with pembrolizumab plus rituximab, the ORR was 80% with an impressively high CR rate of 60%.[64] These data are promising but require confirmation in a larger cohort with long follow-up.

Table 3 lists a selection of investigational drugs targeting the microenvironment.

There is no doubt that the armamentarium of new compounds in FL will change the treatment landscape, but efficacy and toxicity of most agents have still to be verified in larger cohorts and will require a long follow-up. As suggested for ibrutinib, venetoclax, or lenalidomide, single activity especially in the relapse situation may be limited. On the other hand, combinations of novel agents demonstrate new toxicities. A phase I trial combining idelalisib, lenalidomide, and rituximab stopped early.[65] Similarly, the combination of ibrutinib, lenalidomide, and rituximab also generated unexpected side effects.[66]

Requirements for future clinical trials

A significant number of new compounds for FL have already been tested in clinical studies, mainly phase I and phase II protocols, and many more await clinical testing.

In first line therapy, early identification of patients with a potentially aggressive course is required. As we learned from the National LymphoCare study, relapse in the first 24 months after first-line therapy significantly influences overall prognosis. The early identification of such patients and improving the initial therapeutic approach represents an important goal of future clinical trials, and both PET and MRD assessments after induction therapy may contribute to this. These patients may not benefit from immunochemotherapy alone and have the

Table 3

Selected Investigational Drugs in Follicular Lymphoma: Targeting the Microenvironment

Agent	Target	Clinical Study	N	Response	Durability	Refs.
Lenalidomide	"Immunomodulation"	Phase III, frontline, +rituximab	513	CR 48%[a]	3-yr PFS 77%[a]	Morschhauser et al[61]
		Phase IIIb, R/R[b], +rituximab	133	ORR 66%, CR 36%	1-yr PFS 70%	Andorsky et al[63]
CC-122	Cereblon	Phase Ib+ Obinutuzumab	29	ORR 76%, CR 41%	Median PFS 21.2 mo	Michot et al[78]
Nivolumab	PD-1	Phase Ib, R/R	10	ORR 40%, CR 10%	23-mo PFS 75%	Lesokhin et al[79]
Pembrolizumab	PD-1	Phase II, R/R, +rituximab	15	ORR 80%, CR 60%	—	Nastoupil et al[64]

CR = complete remission, ORR = overall response rate, PD = programmed cell death, PFS = progression-free survival, R/R = relapsed/refractory.

[a] Results similar to rituximab + chemotherapy.

[b] ≥ Two lines of therapy.

greatest need for incorporation of innovative compounds. Clinical studies have identified biomarkers for early progression that can identify therapeutic targets which should lead to more tailored approaches with or without chemotherapy.

On the other hand, many patients have an indolent course of the FL, some of whom may be overtreated with current immunochemotherapy. Protocols should therefore focus on the reduction of toxicity in this subset, in order to maintain or even increase efficacy in an economically acceptable way.

In the relapse setting, clinical studies should focus on the improvement of the TTNT, which could mean the addition of new agents to existing protocols or the use of new treatment approaches without chemotherapy. The definitive role of hematopoietic stem cell transplantation has to be reevaluated in the light of these of these advances.

In conclusion, immunochemotherapy or monoclonal antibodies alone in selected patients remains standard of care in front-line therapy and at first relapse in FL patients, but promising new compounds have the potential to increase efficacy if added to current regimens and could replace them. Toxicity, quality-of-life and the costs of new approaches have also to be addressed in long-term follow-up both with existing and novel regimens. The delineation of optimal therapy for the individual patient still remains a major challenge in the design of future clinical trials.

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