REVIEW

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Advancements in the Management of Follicular Lymphoma: A Comprehensive Review

Foliküler Lenfoma Yönetiminde Gelişmeler: Kapsamlı Bir Derleme

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Abstract
Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin lymphoma in Western countries. While FL is generally incurable, standard initial therapies are associated with high response rates and durable remissions for most patients. In addition, novel targeted agents and immunotherapies are changing the treatment algorithm for patients with relapsed or refractory disease. This review discusses initial staging, prognosis, and treatment options for newly diagnosed and relapsed/refractory FL. Initial treatment options for FL include active surveillance, radiotherapy, rituximab monotherapy, and chemoimmunotherapy. Staging with PET/CT and bone marrow biopsy is crucial for identifying early-stage patients. Most patients with FL will receive chemoimmuntherapy as initial treatment with options including rituximab or obinutuzumab plus CVP, CHOP, bendamustine, or lenalidomide. No significant differences in overall survival have been observed in randomized studies comparing these regimens. Maintenance therapy with rituximab or obinutuzumab in responders to initial chemoimmunotherapy improves progression-free survival. For relapsed/refractory FL, treatment options include chemoimmunotherapy, lenalidomide-based regimens, tazemetostat, chimeric antigent receptor (CAR) T cell therapy (axicabtagene ciloleucel and tisagenlecleucel) and CD3/CD20 bispecific antibodies (BsAbs). Given encouraging outcomes with CAR T cell therapy and BsAbs, multiple trials are testing these highly active agents in earlier lines of therapy and among high-risk patients with early relapse after frontline chemoimmunotherapy. Additonal studies and follow-up are needed to understand how these novel agents may further change treatment algorithms for FL.
Key words: Follicular Lymphoma, Management, Review

Özet
Foliküler lenfoma (FL), Batı ülkelerindeki indolent non-Hodgkin lenfomanın en yaygın alt türüdür. FL genellikle tedavi edilemez olsa da, standart başlangıç tedavileri çoğu hastada yüksek yanıt oranları ve sürdürülebilir remisyonlarla ilişkilidir. Ayrıca, yeni hedefli ajanlar ve immünoterapiler, relaps veya refrakter hastalığı olan hastaların tedavi algoritmalarını değiştirmektedir. Bu derleme, yeni tanı konmuş ve relaps/refrakter FL için başlangıç evrelemesi, prognoz ve tedavi seçeneklerini tartışmaktadır. FL için başlangıç tedavi seçenekleri arasında aktif gözetim, radyoterapi, rituksimab monoterapisi ve kemoimmünoterapi yer almaktadır. PET/BT ve kemik iliği biyopsisi ile evreleme, erken evre hastaları tanılamak için kritiktir. FL hastalarının çoğu, rituksimab veya obinutuzumab ile birlikte CVP, CHOP, bendamustin veya lenalidomid gibi seçenekleri içeren kemoimmünoterapiyi başlangıç tedavisi olarak alacaktır. Bu rejimleri karşılaştıran randomize çalışmalarda genel sağkalımda önemli farklar gözlemlenmemiştir. Rituksimab veya obinutuzumab ile idame tedavisi, başlangıç

kemoimmünoterapisine yanıt veren hastalarda progresyonsuz sağkalımı artırır. Relaps/refrakter FL için tedavi seçenekleri, kemoyimmünoterapi, lenalidomide tabanlı rejimler, tazemetostat, kimerik antijen reseptörü (CAR) T hücre terapisi (aksikabtagen sileulesel ve tisagenlecleucel) ve CD3/CD20 bispesifik antikorlar (BsAb'ler) içermektedir. CAR T hücre tedavisi ve BsAb'lerle umut verici sonuçlar alındığından, bu yüksek etkili ajanların tedavi algoritmalarını FL'nin ön tedaviden sonraki erken relapsı olan yüksek riskli hastalarda test etmek için birçok çalışma yapılmaktadır. Bu yeni ajanların FL için tedavi algoritmalarını nasıl daha fazla değiştirebileceğini anlamak için ek çalışmalar ve takip gereklidir.

Introduction

Follicular lymphoma (FL) represents the prevailing subtype among indolent lymphomas within Western nations, accounting for approximately 20-30% of all non-Hodgkin lymphoma cases [1]. FL often manifests a protracted clinical course and is frequently diagnosed in advanced stages, with fewer than 10% of patients presenting at stage I-II upon diagnosis. Approximately 70% of patients have marrow involvement at diagnosis. In contrast to more aggressive lymphomas, the occurrence of B symptoms and elevated lactate dehydrogenase (LDH) levels is detected in fewer than 20% of patients [2].

FL arises within germinal centers and is characterized by the presence of t(14;18) translocation, which leads to aberrant BCL2 expression. The neoplastic cells express CD20, CD10, BCL2 and BCL6 by immunohistochemical staining. Histologically, FL is graded on a scale from 1 to 3, primarily based on the quantification of centroblasts. Grade 3 is further subclassified into A and B categories, with grade 3B being categorized and treated as diffuse large B-cell lymphoma (DLBCL). Typically, grade 1-2 FL exhibits an indolent clinical course. The outcome of patients with grade 3A disease is controversial with some series demonstrating similar behavior as grade 1-2 and others suggesting a more aggressive course.[3] In the WHO 5th classification, follicular lymphoma is divided into 3 groups: classic FL (cFL), follicular large B-cell lymphoma (FLBL) and FL with uncommon features (uFL). [4] The revised WHO 5th edition no longer mandates grading given the unclear impact on clinical behavior therefore grade 1-3A disease now classified as cFL.[4] Grade 3B follicular lymphoma is a distinct entity, typically lacking CD10 expression and t(14:18)[5] and has more aggressive clinical course. According to WHO 5th edition the subtype of FLBL largely equals FL grade 3B. [4] We will focus our discussion on cFL in this review.

Some uncommon FL subtypes are associated with unique presentations and clinical courses. FL with 1p36 deletion (typically in the absence of t(14;18) translocation) typically presents with diffuse follicular involvement, predominantly affecting inguinal lymph nodes. Histologically, these cases primarily align with grade 1-2 structure and exhibit an indolent clinical course, thus warranting treatment in a manner similar to conventional FL [6]. Pediatric-type FL represents a distinct entity, frequently associated with localized head and neck lymph node involvement. Notably, these cases lack BCL2 rearrangement and t(14;18) translocation, and they generally carry a favorable prognosis [7].

FL is associated with a risk of transformation to diffuse large B-cell lymphoma. In one large study, the risk of transformation within 5, 10, and 15 years stood at 17%, 28%, and 37%, respectively [8]. At the time of transformation, patients often present with rapidly enlarging lymph nodes, elevated LDH levels, B symptoms, hypercalcemia, extra-nodal involvement beyond the bone marrow. Biopsy is important to document transformation, and positron emission tomography (PET) imaging can be helpful at identifying sites to biopsy.

Prognosis

The incorporation of rituximab into FL therapy has led to a significant improvement in overall survival, with an estimated 10-year survival rate of 80%. However, lymphoma-related mortality remains at 10% after a decade, likely reflecting histological transformation [9]. Multiple clinical scores have been established for prognostic assessment in FL, including FLIPI and FLIPI-2. The FLIPI-2 score is comprised of 5 factors (age over 60 years, bone marrow involvement, hemoglobin levels below 12.0 g/dL, the largest diameter of the largest affected lymph node exceeding 6 cm, and serum beta-2 microglobulin levels surpassing the upper limit of normal) and was specifically developed for patients receiving rituximab-based therapies while excluding patients on active surveillance [10,11]. 5-year progression-free survival rates were 98%, 88%, and 77% for patients with low-risk, intermediate-risk, and high-risk, respectively, based on FLIPI-2 [11]. More recently, the m7-FLIPI score was devised to incorporate genomic alterations. Seven genes frequently mutated in FL (EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, and KART11) were identified as prognostic in patients treated with RCHOP or RCVP. The 5-year failure-free survival rates were 77% for the low-risk group and 38% for the high-risk group [12]. The m7-FLIPI score, however, lacks predictive utility in patients receiving bendamustine or obinutuzumab-based treatments, limiting its clinical applicability [13]. Other prognostic score, comprising only 2 simple parameters (bone marrow involvement and β2-microglobulin [β2m]) called the PRIMA-PI (PRIMA-prognostic index), comprised 3 risk categories: high (β2m > 3 mg/L), low (β2m ≤ 3 mg/L without bone marrow involvement), and intermediate (β2m ≤ 3 mg/L with bone marrow involvement). Acoording to this index five-

year PFS rates were found 69%, 55%, and 37% in the low-, intermediate-, and high-risk groups, respectively (P < .0001). [14]

Numerous studies have evaluated the prognostic value of end-of-treatment PET, demonstrating their correlation with both progression-free survival (PFS) and overall survival (OS) in FL patients [15-17]. In one study of patients treated with R-CHOP, those with a negative end-of-treatment PET achieved a 2-year OS rate of 100%, in contrast to 88% in patients with positive PET CT [16]. Another study in 202 patients showed a 3-year PFS rate of 66% for those with negative PET CT, compared to 35% in PET positive patients. for those with positive findings [17]. In addition to the prognostic importance of PET at the end of treatment, the relationship between total metabolic tumor volume (TMTV) calculated before treatment and PFS has been shown in studies. [18,19] FL patients enrolled in the FOLL12 trial, 5-year PFS was found significantly lower for patients with high vs low TMTV (60% vs 75% p<0.001) [18]. Similarly, in the RELEVANCE study, a concluded that baseline TMTV is predictive of PFS, independently of FLIPI.[19]

The most consistent predictor of OS in FL patients is disease progression within 24 months (POD-24) of initial therapy. After R-CHOP treatment, the 5-year OS rate was 50% for patients experiencing early progression and 90% for those without early progression [20]. Transformation to aggressive lymphoma, which may have been present at the time of initial therapy, contributes to the poorer outcome in patients with POD24.

Initial therapy of stage I/II FL

The initial treatment options for early-stage FL include active surveillance, radiotherapy, rituximab monotherapy, and chemoimmunotherapy. Importantly, no difference in survival has been observed among these treatment modalities in early-stage disease.

Staging with PET/CT and bone marrow biopsy are important to identify early stage patients before giving treatment decision. [21] 24-30 Gy dose of radiotherapy is a standard of care in early stage FL with disease that can be targeted using a feasible radiotherapy field. Outcomes in patients with stage I are superior compared to stage II disease with an estimated 5-year freedom from progression of 74.9% for stage I and 49.1% for localized stage II [22]. In the context of early-stage disease, 5-year and 10-year OS rates with radiotherapy range between 82-96% and 64-83%, respectively [22-29]. The likelihood of disease recurrence after 10 years is low [23,25]. Tumor diameter is another significant factor influencing outcomes in patients receiving radiotherapy, with larger tumor sizes at the outset of radiotherapy associated with reduced PFS [24,25]. Although retrospective in nature, studies have indicated that the addition of rituximab to radiotherapy or chemotherapy with rituximab results in a notable improvement in PFS but has no discernible impact on OS [26-30].

Particularly in cases of non-contiguous stage II disease and other scenarios, including abdominal disease, where radiotherapy may not be suitable, active surveillance, rituximab monotherapy, or chemoimmunotherapy represent viable options. [27-29]. Studies have shown that 7.5-year and 5-year OS are 100% with rituximab monotherapy in early-stage disease. [27,29] On the other hand, the 7.5-year overall survival rate of 74% with chemoimmunotherapy shows that this treatment is an option for this patient group. [29] In another study, median PFS could not be reached with chemoimmunotherapy after 57 months of follow-up [30].

Recent studies have also demonstrated that the "watchful and waiting" (W&W) strategy typically applied in patients with advanced-stage FL and low tumor burden, can be extended to certain individuals with early-stage disease [29-31]. Advani et al. reported 5-year and 10-year OS rates of 97% and 66%, respectively, for patients managed with the W&W approach [31].

In light of the collective data, radiotherapy emerges as a compelling choice for confirmed stage I disease. However, for other patients with early-stage FL, treatment decisions should be made on a case-by-case basis, taking into account various clinical factors and patient preferences [32].

Initial therapy of advanced stage FL

In advanced stage FL patients, immediate treatment decision is made based on tumor burden according to GELF (The Groupe d'Etude des Lymphomes Folliculaires) criteria therapy (Table 1). Patients who meet one of the GELF criteria are considered to have high tumor burden. In asymptomatic patients with low tumor burden, available evidence does not demonstrate superiority of immediate treatment over active surveillance. The decision of when to treat patients with follicular lymphoma is subjective, as is the definition of low burden disease. [33].

Active surveillance

In a randomized phase III study with a median of 16 years of follow-up, chlorambucil did not impact OS compared to observation in asymptomatic patients [34]. Similarly, studies conducted with rituximab have concluded that asymptomatic patients can be safely observed without immediate treatment. In one prospective study, patients were randomized into three groups: follow-up without treatment, rituximab induction only, and rituximab induction plus maintenance. 3-year progression-free survival was 60% (95% CI 49–71) in the rituximab induction group, which was significantly different from the other two arms: HR 0·53 (95% CI 0·32–0·87; p=0·011) for the comparison between maintenance rituximab and rituximab induction and HR 0·55 (0·37–0·83; p=0·0034) for the comparison between rituximab induction and watchful waitingbut there was no

difference in 3-year OS rates (94%, 97%, vs 96%)respectively. [35] A retrospective study, which included a majority of patients with low tumor burden (80%), found that the 5-year OS rates were similar for patients who did not receive treatment compared to those who received rituximab-based treatment [36]. A large retrospective analysis of 1754 patients showed no difference in PFS or OS following first and second line therapy in patients managed with active surveillance, rituximab monotherapy, or chemoimmunotherapy. Patients with grade 3 histology, anemia, elevated lactate dehydrogenase, extra-nodal involvement, B symptoms, or a performance status ≥1, were more likely to receive chemoimmunotherapy. [37] The cumulative evidence presented in these studies strongly supports a W&W strategy as a favorable option for asymptomatic patients with with a low tumor burden.

In patients requiring treatment the primary therapeutic approach typically involves combining chemotherapy with anti-CD20 therapy. Single agent rituximab is also a reasonable therapeutic approach, particularly in patients with comorbidities or non-bulky diseaseand in individuals who prefer to delay or avoid exposure to cytotoxic chemotherapy. With regard to OS, no treatment approach demonstrates superiority over others. Therefore, the choice of initial therapy should be tailored based on individual patient factors.

Chemoimmunotherapy

Initial chemoimmunotherapy options in FL (Table 2) include rituximab or obinutuzumab plus CVP, CHOP, bendamustine, or lenalidomide. None of the randomized studies comparing these regimens has demonstrated an improvement in overall survival, likely due to the availability of highly effective subsequent lines of therapy. RCHOP is associated with increased PFS compared with RCVP [38,39]. In a randomized study comparing RCHOP to BR in indolent B-cell lymphoma and mantle cell lymphoma, the median PFS of RCHOP was 31 months compared with 69 with BR (hazard ratio 0.58, 95% CI 0.44-0.74; p<0.0001). [40] In a study designed to show superiority of lenalidomide plus rituximab over combination chemotherapy with the majority of patients receiving RCHOP, there was not a significant difference in PFS with a 6-year PFS of approximately 60% in both arms. [43,44] More recently, obinutuzumab plus chemotherapy was compared to rituximab plus chemotherapy, with all patients receiving maintenance therapy for 2 years. PFS at seven years was 53% versus 57% in patients receiving obinutuzumab containing regimens. Patients receiving bendamustine containing regimens experienced higher rates of toxicity including infection during maintenance. [45-46]

Maintenance therapy

Maintenance therapy with rituximab or obinutuzumab in patients responding to initial chemoimmunotherapy is associated with improved PFS, again without evidence of superior OS, but comes at the cost of increased toxicity in the form of delayed neutropenia and infection. In the PRIMA trial, FL patients who received chemoimmunotherapy followed by rituximab maintenance therapy achieved a median PFS of 10.5 years compared to 4.1 years in the observation arm (hazard ratio, 0.61; 95% CI, 0.52 to 0.73; $P < .001$) [48]. In addition, a retrospective analysis of maintenance rituximab after BR in the BRIGHT study demonstrated a significant improvement in PFS with a trend towards improved OS [49]. In another study, the outcome of rituximab maintenance after BR treatment was examined retrospectively as real-world data. The authors of this study found that patients in complete remission did not exhibit an improved duration of response with rituximab maintenance compared to those who reached partial remission after ≥4 cycles of BR. (3-year DOR for patients who achieved a PR was 80% and 45%, with and without rituximab maintenance respectively [50]. Considering the retrospective nature of the studies, rituximab maintenance after BR treatment should be decided on a patient basis. For patients who received obinutuzumab-based therapy during the induction phase, maintenance therapy with obinutuzumab for 2 years is also associated with improved PFS compared to rituximab [45].

Single agent rituximab

For patients with lower burden disease, comorbidities or a preference to avoid chemoimmuntherapy, single agent rituximab is a reasonable therapeutic option. In a study that included both previously untreated and relapsed patients receiving rituximab for four weekly doses followed by an additional 4 doses of extended induction every 2 months, the treatment naïve patients experienced a median PFS of 6.6 years and 10 year PFS of 42% [51].

A recent study compared single agent intravenous rituximab to subcutaneously (SC) administered rituximab in patients with low burden follicular lymphoma. In both arms, patients received four weekly doses followed extended induction for 4 doses every 2 months. Interesting, SC administration was associated with improved PFS at 4 years of 58% versus 41%. [52]

TREATMENT OF RELAPSED/REFRACTORY DISEASE

While frontline treatments for FL are associated with high response rates, most patients will eventually relapse. Time to relapse is an important prognostic marker. Approximately 20% of patients receiving frontline chemoimmunotherapy will progress within 24 months of initial treatment (POD24) and have inferior OS compared to other patients with FL [53]. Diagnostic confirmation at relapse (to exclude transformation to an aggressive lymphoma) is a critical consideration, particularly for POD24 patients, who appear to be at higher risk for transformation[54]There are multiple reasonable treatment options for relapsed/refractory FL. Asymptomatic patients can be managed with observation, similar to the frontline setting. Radiation is an appropriate treatment for selected patients with localized relapse or a single symptomatic site of recurrence.

When systemic treatment is indicated, rituximab monotherapy or chemoimmunotherapy have been the historical standards. Rituximab re-treatment is more likely to be effective among patients who had durable remissions to frontline therapy [55]. BR and RCHOP are the most commonly used chemoimmunotherapy regimens in the relapsed/refractory setting. For patients with rituximab-refractory disease (defined as no response to or progression following any rituximab-contaning regimen within 6 monsth of the last rituximab dose), use of obinutuzumab should be considered based on the phase III GADOLIN trial, which demonstrated improvement in OS with obinutuzumab-based chemoimmunotherapy[56]. Patients achieving CR or PR to second-line or subsequent chemotherapy can be treated with extended therapy. In a phase III randomized trial involving patients with relapsed or resistant disease who responded to CHOP or RCHOP induction therapy, rituximab maintenance therapy significantly enhanced median PFS compared to observation alone (4 years versus 1 year; $P < .001$). After a median follow-up period of 6 years, the 5-year Overall Survival (OS) rate did not exhibit a statistically significant difference between the study arms, with rates of 74% and 64% respectively. [57] Other study study examining the efficacy of rituximab maintenance versus rituximab retreatment at disease progression in patients with indolent lymphomas who had previously undergone chemotherapy (n = 114), rituximab maintenance significantly extended PFS compared to rituximab retreatment (31 months versus 7 months; $P = .007$). However, despite the significant difference in PFS, the duration of benefit was similar in both treatment groups, with 31 months observed in the maintenance group and 27 months in the retreatment group. [58]. Like rituximab, obinutuzumab can also be used for maintenance in relapse-refractory patients. In the GADOLIN study, the implementation of obinutuzumab maintenance therapy subsequent to second-line treatment involving bendamustine plus obinutuzumab resulted in an enhancement of PFS among patients who had displayed refractoriness to rituximab. [56]

Stem cell transplantation

With the approval of multiple novel therapies, including CAR-T cells and bi-specific antibodies, the use of stem cell transplantation has declined, particularly in countries where these agents are approved. Both autologous and reduced intensity allogeneic stem cell transplant have been used in the relapsed/refractory setting. Consolidation in 2nd remission with autologous stem cell transplantation (ASCT) can also be considered for high-risk patients (i.e. POD24). Two retrospective studies suggested an OS benefit for consolidative ASCT [59,60] , however, these studies were performed prior to the availability of many of the novel therapies discussed below. In a large retrospective study comparing outcomes in 518 patients who were initially treated with rituximab containing therapy between 2000 and 2012, autologous transplantation was associated with lower rates of non-relapse mortality but higher rates of relapse [61]. Overall survival was improved with autologous transplant in the first 2 years, but allogeneic transplant resulted in superior survival and lower rates of secondary malignancies beyond 2 years.[61] For patients with chemotherapy sensitive disease and adequate bone marrow reserve, autologous transplantation may lead to durable disease control in a subset of patients. Allogeneic transplantation remains a therapeutic option for patients who have relapsed after CAR-T or other novel agents or in settings where these agents are not available.

Treatment of relapsed/refractory FL is rapidly changing with approvals for multiple novel targeted and immunotherapy agents.

Novel agents in relapsed/refractory FL

Lenalidomide

Lenalidomide is an immunomodulatory agent that has multiple mechanisms of action including inducing changes in T-cell subsets and function by reducing regulatory T-cells and activating CD8 positive cells [62]. As a single agent in relapsed and refractory FL, lenalidomide was associated with Overall Response rates (ORR) and Comlette Response rates (CRR) of 27% and 9% respectively, with a median PFS of 4.4 months in a small phase 2 study [63]. In combination with rituximab, responses are improved with ORR of 65-78% and CR rates of approximately 35-40% [64,65]. In addition, the GALEN study tested lenalidomide plus obinutuzumab for one year, followed by maintenance lenalidomide for one year and obinutuzumab for 2 years [66]. The ORR and CR rates were 79% and 38% with a 2-year PFS of 65%.

The AUGMENT randomized phase 3 study established rituximab plus lenalidomide as standard second line approach in FL. 358 patients with FL (82%) or marginal zone lymphoma (MZL) (18%) received rituximab once weekly for 4 doses during cycle 1 followed by day 1 on cycles 2-5 in combination with lenalidomide (20 mg days 1-21 of a 28 day cycle) or placebo for 12 cycles. The median PFS strongly favored the lenalidomide arm at 39.4 versus 14.1 months. In terms of toxicity, leukopenia, rash, and infection were more common in the lenalidomide arm [67].

Tazemetostat

EZH2 is an epigenetic modifier that is important in the germinal center reaction. Approximately 20% of cases of FL harbor gain of function mutations in EZH2. Tazemetostat is an oral EZH2 inhibitor that was tested in patients with relapsed/refractory FL in a multi-center phase 2 study. In the EZH2 mutated cohort (n=45) who had received a median of 2 prior lines of therapy, the overall and complete response rates were 69% and 13%,

respectively. In the EZH2 wild type group (n=54), patients had received a median of 3 prior lines of therapy, and achieved ORR and CRR of 35% and 4%, respectively. Interestingly, the median PFS in the two groups was similar at 13.8 versus 11.1 months. High grade cytopenias were rare and the serious adverse event rate was 4% [68].

Tazemetostat is a reasonable option in patients with non-bulky disease or those who are not candidates for more aggressive therapy. Given the drug's favorable toxicity profile, it is currently being studied in combination with other novel agents.

PI3K inhibitors

The PI3 kinase inhibitors idelalisib (which targets the delta isoform), and duvelisib (which targets the gamma and delta isoforms), were voluntarily withdrawn from the market in 2021 given safety concerns that arose in long term follow-up of clinical trials in patients with chronic lymphocytic leukemia. The contribution of these agents to excess mortality is not clear, given the impact of subsequent lines of therapy, as well as COVID-19 infection. Both agents have been associated with colitis and risk of infection. The original approvals in FL were based on phase 2 studies which demonstrated ORR/CR of 57%/14% for idelalisib and 42%/1%for duvelisib [69,70]. The median PFS rates were 11.8 and 9.5 months respectively.

The only remaining drug in this class is copanlisib, a pan-PI3 kinase inhibitor, which unlike idelalisib and duvelisib is administered intravenously. In terms of efficacy, the ORR in the phase 2 study was 60% with median PFS of 12.5 months [71]. The major toxicities of this agent are hypertension and hyperglycemia, which are typically managed with calcium channel blockers and metformin. For patients without diabetes or uncontrolled hypertension, copanlisib is generally well tolerated and is an option for patients who can manage the frequency of infusions (weekly for 3 weeks with a one week break).

BTK inhibitors

As single agent therapy in relapsed/refractory FL, ibrutinib was associated with a disappointing ORR of 37.5% with CR rate of 12.5%. [72] The median PFS was 14 months and 2-year PFS rate was 20.4%. In combination with rituximab, however, the 30-month PFS was 67%. [73] In the recently published randomized phase 2 ROSEWOOD study, 217 patients received either obinutuzumab monotherapy or obinutuzumab plus zanubrutinib [74]. The ORR and CRR were 46% versus 69% with CRR of 19% versus 39%, respectively. The median PFS were 10.4 and 28 months, respectively. Rates of major bleeding and atrial fibrillation in the combination arm were low at 3% and 1%. Based, on these results, the phase III MAHOGANY trial is comparing zanubrutinib and obinutuzumab to lenalidomide and rituximab in patients with R/R FL or MZL.

Immunotherapies – CAR T cell therapy and bispecific antibodies

Novel forms of immunotherapy are quickly changing the treatment landscape of R/R FL. In the past three years, the FDA approved two CD19 chimeric antigen receptor (CAR) T cell products– axicabtagene ciloleucel (axi-cel) and tisagenlecleucl (tisacel). In addition, the first CD3/CD20 bispecific antibody (BsAb), mosunetuzumab, was approved for FL earlier this year. Additional approvals for CAR T cells and BsAbs in FL are expected soon, and numerous clinical trials are underway to determine the optimal treatment settings and strategies to best use these highly effective drugs.

CAR T cell therapies

While initial FDA approvals for CD19-directed CAR T cells were issued for patients with DLBCL, ORRs among patients with FL have been consistently higher than those seen in DLBCL or other B-cell NHLs. In addition, rates of high-grade cytokine release syndrome (CRS) and immune-effector cell associated neurotoxicity syndrome (ICANS) also appear to be lower in FL [75-79]. ZUMA-5 was a phase II trial testing axi-cel in patients with either FL or MZL who had relapsed after two or more prior lines of therapy (including a CD20 mAb and an alkylator). Among 124 patients with FL, the overall and complete metabolic response rates were 92% and 77%, respectively [76]. CRS was observed in 78% of patients, but grade 3+ CRS only occurred in 6% of patients. ICANs was also observed frequently, but was primarily low-grade (any grade ICANS 56%, grade 3+ 15%). Responses appear durable with a median PFS of 40.2 months, but longer follow-up is needed to determine if some patients may be cured with this approach [80]. Tisa-cel was studied in a similar patient population in the phase II ELARA trial. Among 98 patients, the ORR was 86% and the CMR was 69%. Tisa-cel appeared to have a more favorable safety profile than axi-cel with lower rates of CRS (any grade 49%, grade 3+ 0%) and ICANS (any grade 37%, grade 3+ 4%) [81]. With a median follow-up of 28.9 months, the 2-year PFS in this trial was 57%. While lisocabtagene maraleucel (liso-cel) is not yet approved for FL, it has also demonstrated encouraging results in patients with R/R FL. The phase II TRANSCEND-FL study tested liso-cel among patients with 2 or more prior lines of therapy or as 2nd line treatment in patients with POD24. Among 107 patients receiving liso-cel as 3rd line or later therapy, the overall and complete metabolic response rates were 97% and 94%, respectively. (Results for POD24 patients receiving liso-cel as 2nd line therapy have not yet been reported). CRS was observed in 58% of patients (including 1% with grade 3+ CRS), while only 15% of patients experienced ICANS (including 2% with grade 3+ ICANS). While follow-up is limited, responses appear to be durable with a 12-month PFS of 81% [82]. Longer follow-up is needed to determine if the higher complete response rates observed with liso-cel compared to other CD19 CARs might translate into improved long-term disease control.

Based on the excellent outcomes in phase II studies described above, randomized phase III studies are ongoing for axi-cel (NCT05371093) and tisacel (NCT05888493). These trials are comparing CAR T cell therapy to standard of care treatment with either chemoimmunotherapy or lenalidomide-based treatment among patients with R/R FL. It is likely that these trials will demonstrate superior PFS with CAR T cell therapy, but absent an overall survival benefit, they still may not definitely determine the optimal setting for CAR T cell therapy in FL. Unlike in R/R DLBCL where lymphoma-related mortality is high and CAR T cell therapy has a clear curative potential, patients with R/R FL often have less aggressive disease and are fortunate to have other effective treatment options, including CD3/CD20 BsAbs. In the meantime, CAR T cell therapy is an excellent option for patients with FL with aggressive clinical features, particularly if there is concern for occult transformation or for patients who favor a one-time intensive treatment option over continuous therapies.

Bispecific Antibodies

Four different BsAbs targeting CD3 on T cells and CD20 on malignant FL cells are in active development in FL. CD3xCD20 BsAbs are associated with frequent CRS, but significantly lower rates of ICANs compared to CAR T cell therapy. To mitigate the risk of CRS, all four CD3xCD20 BsAbs employ step-up dosing and steroid premedication during treatment initiation, and with these approaches, rates of severe CRS are low (less than 5%). In addition, inpatient monitoring has been required on initial trials for all agents, except for mosunetuzumab. Mosunetuzumab, epcoritamab, and glofitamab have similar dose ramp up schedules with weekly escalating dosing over 3 weeks, while odronextamab uses a more onerous step-up dosing schedule that currently requires 4 hospitalizations and twice weekly doses over a four-week period[73-86]. Across all agents, the timing of CRS seems to be predictable with almost all events occurring during the first 1 or 2 cycles of therapy. Beyond CRS, other common adverse events for CD3xCD20 BsAb include cytopenias and infections, which can be severe (including fatal cases of COVID observed on several trials). In contrast, rates of ICANS and tumor lysis syndrome have been very low [73-86].

Initial trials have shown high response rates for all 4 agents, with ORR ranging from 78%-100% and CRR ranging from 60-75% (Table 3) [83-86]. Importantly, high ORRs have been seen across different FL patient subgroups, including high risk populations, like those with POD24. Follow-up is still limited for these trials, but responses appear durable with the median PFS exceeding 18 months for both odronextamab and mosunetuzumab [84,86]. Similar to trials with CAR T cell therapies, longer follow-up is needed to better understand the durability of responses for this therapy class.

Unlike CAR T cell therapy, CD3xCD20 BsAbs do not require personalized manufacturing. Their easier availability and excellent efficacy/toxicity profiles, make CD3xCD20 BsAbs attractive candidates for combination approaches. Epcoritamab has been combined with lenalidomide and rituximab (R2) among R/R FL patients with encouraging results. Among 111 treated patients with R/R FL, the overall and complete response rates were 98% and 87%, respectively, and the 1-year PFS was 78%. The same combination was tested in a smaller population of patients with untreated FL (n=41) and also yielded very high response rates (ORR 94% CMR 86%) [87,88]. In both trials, treatment was well tolerated without new safety signals, supporting the feasibility of BsAb combinations in FL.

Based on these encouraging results, BsAb-based combinations are being tested across all lines of therapy in FL (Table 4). There are ongoing confirmatory randomized phase III trials for epcoritamab and mosunetuzumab (NCT05409066, NCT04712097). These trials have similar designs which will determine if the addition of a CD3xCD20 BsAb to lenalidomide-based treatment can improved PFS among patients with R/R FL. There are also 7 ongoing phase II trials testing BsAbs as part of frontline therapy either as monotherapy or with various combinations partners including CD20 mAbs, polatuzumab, lenalidomide, and tazemetostat.

Key questions remain about how best to incorporate BsAbs into the treatment paradigm for FL. Should BsAbs be used alone or in combination? What agents are optimal combination partners? Can we identify biomarkers to predict high-grade CRS, and if so, is inpatient hospitalization necessary for most patients during dose escalation? What is the optimal duration of treatment with BsAbs and does it vary based on treatment setting? Will patients who receive time-limited treatment with BsAb benefit from re-treatment at the time of progression? Answering these questions and others will be critical to maximizing the potential benefit of BsAbs for patients with FL.

Conclusion

The treatment landscape for FL is evolving quickly with multiple novel target agents and immunotherapies approved in recent years. The optimal selection and sequencing of these agents is not yet defined and should be personalized based on individual patients characteristics and preferences. Ongoing exploration of bispecific antibodies and CAR T cell therapies has the potential to further transform FL management, however important questions remain underscoring the need for continued clinical research.

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Table 1 GELF criteria
Any mass ≥ 7 cm in diameter
Involvement of ≥ 3 nodes, each ≥ 3 cm in diameter
Presence of B symptoms
Splenomegaly
Compression syndrome
Ascites or pleural effusion
Cytopenias
Leukemia (> 5.0 x 109/L circulating malignant cells)

Table 2. Treatment in high tumor burden patients		
Treatment [Ref]	CR/ORR (%)	Comment
RCVP vs RCHOP vs RFM [38,39]	RCVP 67/88 RCHOP 73/93 RFM 72/98	-3 year TTFs were 46%, 62%, and 59% for the respective treatment groups -3 year PFS rates were 52%, 68%, and 63% (overall P .011) -3year overall survival was 95% for the whole series -8 year overall survival was 83% for the whole series -RFM is significantly toxic -Higer numbers of second malignancies with RFM. - Patients initially treated with R-CVP had a higher risk of lymphoma progression compared with those receiving R-CHOP
BR vs RCHOP [40]	BR 40/93 RCHOP 30/91	- Median follow-up of 45 months, the median PFS was 69 months and 31 months *(P* < .0001), respectively, for BR and RCHOP. -BR was associated with less neutropenia or infections -Secondary malignancies was 8% with BR and 9% with RCHOP - OS 10 year 71% and 66%, respectively, for BR and RCHOP
BR vs RCHOP/RCVP [41-42]	BR 30/99 RCHOP/RCVP 25/94	The medians were not reached for any of the time-to event end points for either the BR or R-CHOP/R-CVP PFS rates at 5 years were 65.5% in the BR and 55.8% in the R-CHOP/R-CVP group. The difference in PFS was considered significant with a hazard ratio of 0.61 Event-free survival and duration of response also favored the BR regimen over R-CHOP/R-CVP OS is the same in all chort Higher secondary malignancies with BR
R+Len vs R+Chemo [43-44]	R+Len 48/61 R+Chemo 53/65	-6 year PFS was 60% and 59% for R+Len and R-chemo, respectively -6 year OS was estimated to be 89% in both groups. -Median PFS and overall survival were not reached in either group -Higher grade 3 or 4 neutropenia and febrile neutropenia of any grade with R+Chemo -Higher grade 3 or 4 cutaneous reactions with R+Len - R+Len provides an acceptable chemo-free alternative.
O+Chemo vs R+Chemo [45-46]	O+Chemo 19,5/88,5 R+Chemo 23,8/86,9	-7year PFS was improved with O+chemo (63.4%) vs R+chemo (55.7%) (p=0.006) -TTNLT was improved with O+chemo vs R+chemo (HR, 0.71 p=0.001), the proportion of pts who had not started their next treatment at 7 years was 74.1% and 65.4%, respectively. -Disease transformation was observed in 4.2% of pts with O+chemo and 5.0% of pts with R+chemo. -7 year OS was similar in both arms, 88.5% with O+chemo versus 87.2% with R+chemo -İncidence of serious AEs was 48.9% with O+chemo (28.2% and 24.4% during induction and maintenance, respectively) and 43.4% with R+chemo (24.6% and 21.7%, respectively). - Serious AEs much more in patients who recieved bendamustine, be cautious during maintenance of O or R if patient received bendamustine. - One of the important outcomes of the GALLIUM study is that O+Chemo reduces the risk of POD24 by 34% compared to the combination of R+chemo.
RCVP: Rituximab, cyclophosphamide, vincristine, prednisone; RCHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RFM: Rituximab, fludarabine, mitoxantrone; BR: Bendamustine plus rituximab; R: Rituximab; Len: Lenalidomide; O: Obinutuzumab; Chemo: Chemotherapy		

Table 3. Results from BsAb trials in FL

[Ref]	Trial	Eligibility	Pts N	ORR/CRR	PFS/OS	CRS	Neurotoxicity	Notes
Mosunetuzumab [84]	Phase II	2+ prior lines including CD20 and an alkylator	90	78%/60%	24m PFS 51.4%	44% any grade	5% any grade No Grade 3+	
Epcoritamab [83]	EPCORE NHL-1		128	ORR 82%				Based on press release only
	Phase I		12	90%/50%				
Glofitamab [85]	Phase I/II	R/R FL grade 1-3A 1+ prior lines of therapy	72 53(monotherapy) 19 (glofitamab + obinutuzumab)	81%/70% 100%/74%	Limited follow-up	In glofit+ob in 79% any grade, 0% grade 3. 1 case of grade 3 CRS among all pts	None	High response rates seen across high risk pt subgroups
Odronextamab [86]	ELM-2 Phase II	R/R FL, grade 1-3A 2+ prior lines including CD20mAb and alkylator	96	81%/75%, consistent across different pt subgroups	Median PFS was 20.2 months	CRS any grade 51%, grade 3+	No ICANs reported with final dose ramp up strategy	More involved dose escalation with doses on cycle 1 D1-2, D8-9, D15-16, and C2D1. 4 hospitalizations required.
Combinations								
Epcoritamab + R2 [87-89]	Untreated		41	94/86%	Early follow-up	51% any grade, no grade 3+	No ICANs	
	R/R		111	98%/87%, similar across high risk subgroups	1-year PFS 78%	Any grade 48%, grade 3+ 2%	2%	

R2: Rituximab plus Lenalidomide; CRS: Cytokine release syndrome

Table 4. Selected Ongoing BsAbtrials				
	Treatment regimen	**Trial size**	**Trial type**	**NCT number**
Untreated Patients				
Epcoritamab	Rituximab, Epcoritamab	N=35	Phase II	NCT05783609
Glofitamab	Obinutuzumab, Glofitamab	N=35 (FL), N=12 MZL)	Phase II	NCT05783596
Mosunetuzumab	Mosunetuzumab monotherapy	N=53	Phase II	NCT05389293
Mosunetuzumab	Mosunetuzumab and polatuzumab	N=34	Phase II	NCT05410418
Mosunetuzumab	Mosunetuzumab and tazemetostat	N=50	Phase II	NCT05994235
Mosunetuzumab	Mosunetuzumab and lenalidomide	N=52	Phase II	NCT04792502
Mosunetuzumab	Mosunetuzumab monotherapy with addition of obinutuzumab and polatuzumabvedotin for non-complete responders	N=42	Phase II	NCT05169658
POD24				
Epcoritamab	Epco-Len	N=60	Phase II	NCT04663347
Mosunetuzumab (MERLIN)	Mosunetuzumab monotherapy	N=80	Phase II	NCT05849857
R/R FL				
Epcoritamab	Epco +R2 vs R2	N=520	Phase III	NCT05409066
Mosunetuzumab	Mosunetuzumab and lenalidomide vs rituximab-lenalidomide	N=400	Phase III	NCT04712097
Mosunetuzumab	Mosunetuzumab and tiragolumab (anti-TIGIT) with or without atezolizumab	N=118	Phase II (includes both FL and DLBCL)	NCT05315713