Divergent paths: management of early relapsed follicular lymphoma

Radhika Takiar,[1] Yasmin Karimi,[1] and Tycel J. Phillips[2]

[1]Department of Internal Medicine, University of Michigan Rogel Cancer Center, Ann Arbor, MI; and [2]Department of Hematology and Bone Marrow Transplantation, City of Hope National Medical Center, Duarte, CA

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma in the United States and Western Europe. Overall outcomes for patients with FL have continued to improve over the last several decades—most notably, with the addition of the CD20 monoclonal antibody rituximab to the treatment armamentarium. More recently, we have seen advances in the management of patients with relapsed/refractory FL with the approval of several new treatments including lenalidomide, axicabtagene ciloleucel, copanlisib, umbralisib, and tazemetostat. Unfortunately, there remains a group of patients for which treatment outcomes, especially overall survival (OS), are suboptimal. This group has been identified as patients who relapse within 24 months (POD24) of completion of chemoimmunotherapy (CIT). Data indicate that patients who relapse within this window have a 5-year OS of around 50%, compared to 80% for those who remain in remission beyond 24 months. POD24 patients have been included and evaluated in the studies of the novel agents mentioned. While not specifically designed to treat this high-risk group, early data suggest that outcomes are not significantly impacted by this designation, unlike CIT. While to date the optimal management of POD24 patients has not been elucidated, the future appears bright with the continued use of the approved agents and several others in clinical development.

LEARNING OBJECTIVES

- Understand how survival outcomes differ between patients who suffer an early relapse of their follicular lymphoma after receiving chemoimmunotherapy compared to those who relapse after 2 years from treatment completion
- Understand the role of disease transformation in patients who suffer an early relapse after treatment with frontline chemoimmunotherapy
- Understand what options are available for patients with relapsed or refractory follicular lymphoma and how the timing of the relapse affects treatment response
- Understand the promising future options for patients with follicular lymphoma, including those who relapse early after treatment

CLINICAL CASE

A 50-year-old man with a past medical history of hypertension and diet-controlled type 2 diabetes presented to the emergency room with a 3-month history of intermittent abdominal pain. A computed tomographic scan revealed a large retroperitoneal mass. This mass was biopsied and revealed a grade 1 to 2 follicular lymphoma (FL). A staging positron emission tomographic (PET) scan revealed additional fluorodeoxyglucose (FDG)-avid nodes in the neck, chest, axilla, and groin, with the highest standardized uptake value reading being 11. Laboratory studies were notable for an elevated beta-2-microglobulin, mild anemia with a hemoglobin level of 11.0, an elevated lactate dehydrogenase level (1.5×upper limit of normal), and mild chronic kidney disease. Given persistent pain, he was started on therapy with bendamustine and rituximab. He completed 6 cycles of therapy without any significant toxicities and achieved a complete remission (CR). He was subsequently transitioned to observation. Twelve months after completion of therapy, the patient again noted abdominal pain and palpated a lymph node behind his left ear. A repeat staging PET scan demonstrated at least stage III disease with at least 1 region with a standardized uptake value reading of 20. A biopsy of an accessible node confirmed recurrent grade 1 to 2 FL. What are the best options for treatment in this patient with early treatment failure?

Authors' perspective: Given that transformation is always a concern for an early relapsing FL patient, a biopsy should be performed, as FL and transformed FL (diffuse large B-cell lymphoma [tDLBCL]) should be treated differently. The optimal method to rule out transformation is through tissue acquisition, with excisional or core needle biopsy resulting in the best diagnostic yields. In patients with multiple areas of relapse, the preferred site for a biopsy is generally either the largest and most accessible node/mass or the area with the highest FDG avidity as reported by PET/computed tomographic imaging. All things being equal, the most FDG-avid area should be pursued over size given the general higher metabolic rate of tDLBCL compared to FL. If a biopsy is not feasible, clinical factors, such as symptoms, growth of lesions, and serum lactate dehydrogenase, can be used to help evaluate for disease transformation.

Given in this particular case that the patient is confirmed to have recurrent FL and not transformed FL, our preference is to enroll the patient in a clinical study; however, if one is not available, then treatment is generally focused on the utilization of noncytotoxic agents. Lenalidomide is generally our preferred first option in this setting given the efficacy and safety results of the AUGMENT study,[1] which lead to the approval of this agent in relapsed/refractory (R/R) FL after 1 previous line of therapy. Additionally, in the case of this patient lenalidomide would be preferred given the concern for chemorefractoriness in a patient who has relapsed this quickly after completion of a frontline chemoimmunotherapy (CIT) regimen.

Background

FL is the second most common lymphoma overall but the most common indolent lymphoma in the US and Western Europe, with an estimated incidence of 13 960 cases per year.[2] The disease has a variable presentation and clinical course. Most patients are diagnosed with FL incidentally through the investigation of other unrelated medical symptoms or alternative medical conditions vs presenting with the typical B symptoms of fever, night sweats, unintentional weight loss, or fatigue. Given the incurable nature of FL, the decision to treat is complex and based on a multitude of factors, including symptoms, disease extent and/or bulk, lab parameters, and patient psychology. Once a decision to treat has been reached, the choice of regimen is the next important step. Given that FL does not have a standard of care, several options can be considered.

Treatment is highly variable and based on the extent of the disease, patient health, and the goal of therapy. Treatment can range from local radiation to more systemic forms of therapy, including the CD20 antibody rituximab or its recently approved biosimilars, with or without chemotherapy. While both localized radiation and single-agent rituximab are effective therapies, the timing of disease recurrence after these treatments does not appear to significantly affect clinical outcomes and is not a major predictor of outcomes to future treatments. This differs from what has been noted in patients treated with CIT, which is a CD20 antibody, either obinutuzumab or rituximab, combined with chemotherapy. Those who relapse early after receiving CIT are noted to have poor long-term survival. Once CIT is initiated, the patient is expected to obtain a deep and often durable response. This generally starts the theoretical remission clock, which, as we discuss, is an important component of long-term survival.

Several CIT regimens are in use today. Together with rituximab (R) or obinutuzumab (G), the chemo regimens cyclophosphamide, adriamycin, vincristine, and prednisone (G/R-CHOP); rituximab, cyclophosphamide, vincristine, and prednisone; or bendamustine (BR/OB) are utilized.[3] Patients can additionally receive an equivalent frontline regimen, rituximab and lenalidomide (R2), based on supporting evidence from the RELEVANCE study (Table 1).[7] Upon receipt of any of these regimens, most patients are expected to have a durable response. Thereafter, we know that responses can be prolonged with implementation of rituximab maintenance therapy compared to clinical observation, but to date no study has demonstrated that maintenance can prolong survival of patients with FL.[8] Additionally, maintenance treatment is associated with both financial burden and health-related toxicity given the cost associated with infusing the drug over the 2-to-3-year maintenance period and the impact rituximab has on B-cell immunity. This is especially notable now in the COVID-19 era, as research indicates that CD20 antibody–induced B-cell

Table 1. Follicular lymphoma outcomes after frontline chemoimmunotherapy

Regimen	ORR	PFS	OS	% Relapsing within 2 years	Transformation
R-CHOP/R-CVP/R-FCM followed by O vs M[8]	100%	51% (M) vs 35% (O) at 10y	80.1% (M) vs 79.9% (O) at 10y	≈20%-25%	40 patients
R-CHOP/CHOP plus ^{131}I-tositumomab[52]	99%/98%	42%/56% at 10y	81%/75% at 10y	Not formally evaluated. Estimate 22%/20% based on PFS curves	N/A
BR[3]	97%	≈74% at 5y*	≈84% at 5y*	≈20%	N/A
BR[5,6]	93.8%	Median 69.5 mo at 48-mo follow-up	71% at 10y	≈20%	N/A
O-chemo[4]	88.5%	80% at 3y	N/A	9.4%	13 patients
R2[7]	84%	77% at 3y	94% at 3y	16%	10/49 patients
O-Len[27]	94%	82% at 3y	N/A	14%	3/10 biopsied patients

*Indolent non-Hodgkin lymphoma.
G/R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; Len, lenalidomide; M, maintenance; N/A, not available; O, observation.

depletion hampers the immune response to the virus.[9] As such, despite current treatment regimens, all patients with advanced disease and most patients with early-stage disease are expected to relapse. The timing of the relapse is variable, but overall survival (OS) for most patients has continued to improve with advances in treatment and supportive care over the last several decades. We have made several attempts to better predict outcomes in patients with FL, as we know that not all patients achieve a durable remission or long-term survival. The prognostic tools currently available in clinical practice have failed to adequately identify the patients who are most at risk for early death.[10,11] Even the newer iterations of an FL prognostic score (m7-FLIPI, PRIMA-PI, POD24-PI) miss the truly high-risk patients and to date are best served for research purposes only.[12-14] The failure to develop an optimal prognostic scoring system has limited our ability to truly identify those who would benefit most from novel agents and/or regimens vs treatment with the current standard regimens. Tumor sequencing has not yet had an impact on routine clinical practice because most of the alterations identified are not easily targeted.[15] What we do know is that about 20% of patients who receive CIT have progression of disease within 24 months (POD24). Early-relapsing FL patients are at greatest risk for poor outcomes and are difficult to identify at diagnosis. Patients with early treatment failure may anticipate a 5-year OS of 50%, compared to a 5-year OS of 90% for those without early treatment failure.[4,16] Of note, a subset analysis of the Gallium study, a randomized study comparing outcomes of newly diagnosed FL patients treated with obinutuzumab chemo vs rituximab chemo,[4] suggests that the utilization of obinutuzumab chemo has a lower incidence of progression within 24 months compared to rituximab chemo, but this has not been validated.

FL relapse 24 months or more from frontline therapy

Treatment in late R/R FL is variable and dependent on the agent received with initial therapy. Options, depending on what was given with initial treatment, include retreatment with the initial regimen, utilization of a different CIT regimen, single-agent rituximab/biosimilar, radiation, noncytotoxic agents (small-molecule inhibitors, immunomodulatory drugs [IMiDs], etc), or clinical trial participation. Asymptomatic patients with late relapse and low disease burden can be observed or treated with single-agent rituximab/biosimilar. For most patients who require therapy, subsequent therapies administered after the initial treatment result in a series of diminishing returns with decreasing efficacy, duration of response (DOR), and OS. This is noted regardless of the second-line (2L) or beyond treatment modality utilized. With the introduction of newer agents, such as autologous anti-CD19 chimeric antigen receptor T-cell therapy (CAR T) and bispecific antibodies, this paradigm might shift. In time, late-relapsing patients who eventually develop disease that is refractory to rituximab and/or refractory to both rituximab and an alkylator (double refractory) tend to be the most difficult to treat outside of early-relapsing FL patients. Several clinical studies are evaluating novel therapies in R/R FL, but none are specifically targeting either rituximab- or double-refractory patients. Further discussion of this patient population is beyond the scope of this article, as the focus is on options for those with early-relapsed FL.

Early relapse/POD24

The high risks associated with POD24 were identified by Casulo et al and recently validated across several clinical trials conducted before and after the introduction of rituximab.[16,17] Unfortunately, there is no valid method to identify these patients prior to initiation of therapy.[18] As the strict definition of POD24 is generally not followed in most publications, we hereafter refer to these patients as early relapsing (ER). We have recently noted that poor outcomes in ER patients are partly due to disease transformation from FL to tDLBCL.[19] This result is supported by historical data demonstrating poor outcomes in previously treated FL that transforms[20,21]; however, recent data suggest that outcomes for tDLBCL patients are better than previously reported.[22] Thus, transformation in these patients should be ruled out prior to the initiation of 2L therapy.

In patients having or suspected of having tDLBCL, treatment should be administered similarly to those diagnosed with de novo DLBCL. As our discussion is on ER patients, the following discussion on the treatment of tDLBCL assumes that the patients have received CIT prior to transformation. Patients who are anthracycline-naive should be treated with R-CHOP, while those who have previously been treated with an anthracycline should receive an alternative regimen that does not include this class of drugs. If a remission is obtained, consolidation with an autologous stem cell transplant (ASCT) should be considered. This distinction in treatment between FL and tDLBCL is important given that DLBCL has a standard of care and does not generally respond to treatments approved for R/R FL. In those with confirmed FL, several options have been demonstrated to provide treatment responses agnostic to the impact of early relapsing disease and/or superior to historical controls. In the upcoming sections, we discuss these treatments in more detail.

Second-line FL

Immunomodulatory agent

Lenalidomide

Lenalidomide is an IMiD that binds to the cereblon E3 ubiquitin ligase complex, resulting in ubiquitination of the transcription factors Aiolos and Ikaros. The drug's effect on Aiolos and Ikaros leads to changes in immune effector cells, most notably an increase in natural killer cell activity. While lenalidomide's impact on the immune system is believed to be the main driver of its antilymphoma activity, there are data suggesting that alternative mechanisms of action also contribute to the drug's activity.[23-26] Lenalidomide combined with either anti-CD20 antibody rituximab or obinutuzumab has clinically proven antilymphoma synergy.[27-29] Lenalidomide and rituximab (R2) was approved for 2L and beyond FL based on the AUGMENT study.[1] This study randomized patients to R2 vs rituximab-placebo. A subset analysis from this trial did not demonstrate a substantial difference in outcomes for those who were ER compared to those who relapsed after 2 years. This combination has been further evaluated in the MAGNIFY study regarding the role of R2 maintenance in FL after R2 induction. A recent update reported an overall response rate (ORR) and CR of 65% and 32%, respectively, for ER patients vs 74% and 46% for those who relapsed after 2 years. This difference extended to progression-free survival (PFS) and DOR, which were reported as 27.4 months and 37 months, respectively, for ER patients vs

Table 2. Outcomes for early-relapsing patients with lenalidomide

Drug	ORR overall	ORR POD24	CR overall	CR POD24	PFS overall	PFS POD24	OS overall	OS POD24
R2 (Augment)[1]	80%	80%	35%	30%	39.4 mo	30.4 mo	95% (2y)	≈90% (2y)
R2 (Magnify)[30]	72%	65%	42%	32%	NR (median)	27.4 mo (median)	N/A	N/A
O-Len[31]	79.1%	70.8%	46.5%	N/A	64.7% (2y)	62.5% (2y)	86.9% (2y)	82.8% (2y)

N/A, not available; NR, not reached.

not reached in patients who did not relapse within 24 months of initial therapy.[30] In a separate study evaluating obinutuzumab together with lenalidomide, at a median follow-up of 2.6 years, no difference in outcomes was observed between ER patients and those who did not relapse within 24 months.[31] Outcomes for ER patients treated with lenalidomide are outlined in Table 2.

CLINICAL CASE (Continued)

Given the documented relapse, the patient was subsequently started on R2. He obtained a partial response after 6 cycles of therapy. Transplantation was discussed but the patient had no full siblings and declined to travel for consideration of ASCT. He subsequently completed 12 cycles of treatment without any improvement in his depth of response, but his symptoms completely resolved. He had no documented laboratory abnormalities. What would be the best approach at this time?

Authors' perspective: The patient achieved a partial response to treatment with R2. While this is not ideal, it is an expected and acceptable response to this treatment. As such the patient would be appropriate for observation vs maintenance. The AUGMENT study did not include maintenance as an option, but this is being evaluated in the MAGNIFY study,[1,30] which will randomize patients to rituximab maintenance vs R2 maintenance. In the current COVID-19 era, the utilization of maintenance therapy in FL has become more nuanced given the impact of rituximab on immunity. Given his initial early relapse and continued evidence of disease after completion of R2, maintenance would likely be our preferred option vs observation to maintain disease control, but the ultimate decision would be affected by patient age, comorbidities, and vaccination status. Another important consideration to the utilization of maintenance is the expected tolerance and availability of third-line (3L) treatment options. Patients without a complete response who are unable to access or tolerate the options discussed in the next section would benefit most from the prolongation of response that maintenance could provide.

Third-line FL and beyond

Targeted agents

Phosphoinositide 3-kinase inhibitors

Phosphoinositide 3-kinase inhibitors (PI3Kis) function in lymphoma by inhibiting the delta isoform alone or together with the gamma or alpha isoforms of phosphoinositide 3-kinase (PI3K), which is part of the PI3K/AKT/mTOR pathway. This pathway is constitutively activated in malignant lymphoma cells and is important to cellular survival and growth. Several inhibitors have been explored in lymphoma, leading to the accelerated approval of 4 drugs for 3L FL and beyond: the selective delta inhibitor idelalisib, the dual delta/gamma inhibitor duvelisib, the dual delta/alpha inhibitor copanlisib, and the delta/casein-1 epsilon inhibitor umbralisib.[32-35] Idelalisib, duvelisib, and umbralisib are all oral agents that are given every day until disease progression or intolerance in FL. Copanlisib is the only drug in this class that is given intravenously. It is administered once weekly for 3 consecutive weeks with 1 week off on a 28-day cycle. Copanlisib was the only agent in the class with a "quasi" built-in holiday; this is important considering that most toxicities in the class are suspected to be related to cumulative exposure to the delta inhibitor. Copanlisib is, additionally, the only PI3Ki that was approved without a black-box warning, as it was not associated with increasing rates of grade 3 or above class-associated adverse events (AEs; pneumonitis, rash, infection, transaminitis) in long-term follow up. It was however, associated with increasing rates of diarrhea. Concurrent colitis was not uniformly studied because colonoscopies were not mandated. Efficacy was similar among all 4 approved agents. The ORR reported from the respective clinical studies ranged from 42.2% to 60.6%, with the median DOR ranging from 10 months to 14.1 months.[32-35]

Unfortunately, while early studies demonstrated impressive time to response and ORR to PI3Ki even in patients with ER disease,[36] this did not translate to a survival benefit. Additionally, utilization of this class of agents has decreased significantly over the last several years due to the toxicity profile of the entire class, which has high rates of colitis, pneumonitis, rash, and infections, likely due to downregulation of regulatory T cells. In fact, umbralisib, duvelisib, and idelalisib recently had their indications for R/R FL removed, leaving copanlisib as the only approved agent. The decision to remove the drugs from the market is due to updated survival data from the early-phase studies, which have indicated a trend toward lower OS in patients exposed to delta inhibitors. Based on these results, the US Food and Drug Administration made the decision to review the class in its entirety and published a manuscript warning of the risks of the entire class. The FDA also indicated that it will not approve another PI3Ki agent in this class without data generated from a randomized phase 3 trial. While the decision of the FDA is understandable, it is also disappointing, as the efficacy of the class is impressive and independent of the timing of relapse in this patient population, based on data from the completed clinical trials. Several new agents in this class were in development prior to the FDA announcement, most of which were exploring maintenance dosing after an initial 8 weeks of full treatment to attempt to maximize efficacy while reducing the rates of AEs noted with

Table 3. Outcomes for early-relapsing patients with other small molecules

Drug	ORR (overall)	ORR (POD24)	CR (Overall)	CR (POD24)	PFS (Overall)	PFS (POD24)	OS
Tazemetostat[39,40]							
MT pop.	69%	63%	13%	N/A	13.8 mo	13.8 mo	N/A
WT pop.	35%	25%	4%	N/A	11.1 mo	5.8 mo	N/A
Idelalisib[32,36]	57%	56.8%	6%	13.5%	11 mo	11.1 mo	N/A
Copanlisib[33]	58.7%	60.3%	20.2%	22.1%	12.5 mo*	11.3 mo	
Duvelisib[34]	42.2%	33%	1.2%		9.5 mo	8.2 mo	77% at 1y*
Umbralisib[35]	45.3%	N/A	5.1%	N/A	10.6 mo	N/A	N/A
Zandelisib[37]	77.8% 94.7%	81.8%	27.8% 26.3%	18.2%	N/A	N/A	N/A

*All subtypes.
N/A, not available.

continuous full dosing.[37] Since the announcement of the FDA decision, only 1 agent is still being explored, zandelisib. This agent is currently being evaluated in patients with R/R FL in an ongoing randomized phase 3 study vs bendamustine-rituximab.

EZH2/tazemetostat

The enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) is mutated in approximately 20% to 30% of FL patients. Its predictive significance is controversial, with some data suggesting that patients who harbor this mutation would be best treated with a CHOP-based chemotherapy regimen vs bendamustine.[38] Given its prevalence and suspected malignant potential, this mutation became a viable target with the approval of the oral inhibitor tazemetostat.[39] This agent was approved in 3L FL or in 2L for those without another viable option based on a completed phase 2 study looking at those with wild-type (WT) and mutant-type (MT) EZH2. With the approval of the agent came a companion diagnostic test to evaluate for the presence of the mutant type. The utility of this test is currently debatable given the high tolerance of the agent, lack of approved options in the 3L setting, and study-reported outcomes, which indicated that while the MT patients had a higher ORR (CR) of 69% (13%) vs 35% (4%) in the WT cohort, this failed to translate into a difference in long-term responses. The median DOR was reported to be 11 months (mutant type) vs 13 months (wild type), while the median PFS was 13.8 months (mutant type) vs 11.1 months (wild type). With respect to those with ER, their ORR in the entire study was lower compared to those who relapsed after 24 months.[40] However, when evaluated based on mutation status, ER does not appear to have an impact on the efficacy of tazemetostat. ER patients with a mutant type had a PFS of 13.8 months vs 5.8 months in WT patients; the low incidence of the mutation itself makes it difficult to translate this information into clinical practice. Given the low yield of actionable mutations in tumor sequencing for FL patients in general and the reported lack of major differences in outcomes in most MT vs WT patients, it is hard to justify testing for EZH2 in all patients. Ideally, tazemetostat should be considered for most R/R FL patients who are frail or cannot tolerate R2, given the lack of options for these patients and the improved safety profile of tazemetostat compared to copanlisib. For other patients the decision between tazemetostat and copanlisib comes down to patient comorbidities. Testing for a mutant type to help select the most appropriate treatment option might best be served in those who have ER disease and have several potential options, including tazemetostat. Overall outcomes of both tazemetostat and all the PI3Kis are summarized in Table 3.

Cellular therapy

Stem cell transplantation

ASCT and, to a lesser extent, allogeneic (allo)-SCT are typically utilized as potentially curative treatments in patients with R/R tDLBCL or de novo DLBCL. Given the short remission following effective CIT, patients with ER FL are presumed to have disease that is chemotherapy refractory. This premise is supported by the reported poor long-term outcomes of ER patients in retrospective studies evaluating responses to subsequent lines of therapy with cytotoxic agents. Nonetheless, how to interpret data regarding the role of allo-SCT or ASCT in ER FL patients is unclear, especially in the case of ASCT, which requires chemosensitive disease to be effective. A retrospective study of patients with R/R FL by the Center for International Blood and Marrow Transplant Research evaluated outcomes of patients who received an ASCT vs a matched sibling donor (MSD) or a matched unrelated donor (MUD). The study indicated that outcomes with either an ASCT or MSD were superior to the historical response rates noted in the nontransplant population. The 5-year OS was significantly higher following ASCT (70%) or MSD SCT (73%) vs MUD SCT (49%; P=.0008). Outcomes in patients who received an ASCT were best if they had received no more than 3 prior lines of therapy prior to transplantation. As would be expected given the impact of graft-versus-host disease, the authors noted that nonrelapse mortality (NRM) was lower with ASCT compared to either MSD or MUD. The complications of an MUD, including graft-versus-host disease, are still the biggest limitations of this procedure and led to an NRM of 33%. Given the reliance of ASCT on chemosensitivity to be successful, this treatment was reported to have the highest rate of disease relapse (58%), but this did not appear to significantly affect OS.[41] Based on this data, the study authors concluded that both ASCT and MSD may be appropriate options for ER patients who respond to pretransplant salvage therapy.

In our opinion, allo-SCT or ASCT is unlikely to play a major role in the future treatment of patients with R/R FL. Currently, nonchemotherapeutic agents and clinical trials are the treatments

most likely to be utilized in the 2L setting for patients with ER disease, which differs from the patient population evaluated in the Center for International Blood and Marrow Transplant Research study. We currently lack any concrete data regarding the benefit of any transplant after receipt of a noncytotoxic agent in FL. Additionally, as discussed in more detail later, other treatments such as CAR T and bispecific (CD20/CD3) antibodies capture patients who would normally be considered for transplantation. We can safely assume with current practice patterns that these treatments will likely be utilized in the 2L or 3L setting in the future. As mentioned, patients undergoing an MUD transplant have a very high NRM. While the NRM is lower with MSD, the treatment still carries a substantial risk of disability or death, and identifying a sibling match remains an issue for most patients. With those concerns, MSD is not heavily utilized now, and its future role is unlikely to expand. Some academic centers are still likely to consider MSD given its curative potential for younger patients afflicted with this disease.

Chimeric antigen receptor T-cell therapy

CAR T is a cellular therapy that harvests a patient's T cells and transduces them with a CAR to improve the recognition of CD19 on the surface of the malignant B cell. These cells are then expanded and infused back into the patient.[42] This treatment has significantly improved outcomes in B-cell lymphoma with the approval of 3 CAR T products in DLBCL and the recent approval of the CAR T product axicabtagene ciloleucel (axi-cel) for R/R FL after 2 prior lines of therapy.[43] The Zuma-5 study, which led to this approval, demonstrated that axi-cel led to an impressive clinical response, with a reported ORR and CR of 94% and 66%, respectively, in patients with FL. The ORR of ER patients was equivalent to the ORR of patients without ER, demonstrating that this treatment modality is likely agnostic to this prognostic factor, although the study was not powered to detect a difference between these 2 groups.[44] Recently, the CAR product tisagenlecleucel (tisa-cel) was approved for R/R FL. Unlike axi-cel, tisa-cel utilizes a 4-1BB costimulatory domain, which is believed to induce a slower expansion of the engineered T cells compared to the CD28 costimulatory domain utilized in the axi-cel construct. This difference may potentially explain the differing efficacy profile between the 2 agents. Tisa-cel was reported to have an ORR and CR of 86.2% and 69.1%, respectively, in study patients with R/R FL. The study did note that the CR rate in patients with early relapse (59%) was lower compared to those with a late relapse (87.9%). PFS at 12 months was 67% for all patients and 85.5% for those who obtained a CR. The study has not yet reported if there is a PFS difference in those with ER disease.[45]

CAR T is unique from the other drug classes mentioned previously. CAR T is a one-time treatment with restricted availability (approved CAR T centers only) and a side-effect profile notable for unique toxicities such as cytokine-release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), both of which are not seen in any other approved agents. CAR T's limited availability and AE profile currently are the biggest barriers to expanding this treatment modality in R/R FL. Moving forward, the key to CAR T development in FL will be tied to improved tolerance, DOR, and accessibility. If durable responses are noted with CAR T in the R/R setting, this treatment could be considered for an earlier line of therapy. CAR T is not likely to make a major impact in frontline therapy because the benefits of the treatment are unlikely to outweigh its clinical and financial toxicity compared to currently available frontline options. The only clinical scenario in which CAR T would likely be utilized as an earlier treatment is in the 2L setting. Currently, the 2L options for ER patients are limited to R2, tazemetostat, and, less likely, CIT. However, CAR T use in 2L is likely to be encumbered by the forthcoming introduction of CD20/CD3 bispecific antibodies into the FL space. These agents will likely have improved accessibility compared to CAR T and are already noted to have impressive single-agent activity in R/R FL. Additionally, several of these agents are currently being explored in earlier lines of therapy in combination with various agents, including lenalidomide. Looking ahead, the route to increased utilization of CAR T depends heavily on 5 things: (1) whether CAR T can induce long-term durable responses and possibly cure FL, (2) whether the frequency and management of AEs can be improved, (3) whether the cost to administer this therapy can be reduced, (4) whether accessibility can be improved, and (5) whether the better overall profile of newer agents make CAR T less desirable. All in all, unlike in DLBCL, CAR T does not have a clear path forward in FL beyond its current indication.

CLINICAL CASE (Continued)

The decision was made to observe the patient. Six months after treatment completion, he again reported abdominal pain, and imaging indicated disease progression. He was started on copanlisib, but the treatment was stopped due to the inability to control his blood sugar. He was then switched to tazemetostat. He tolerated this treatment well, but his disease progressed after 3 months of therapy. He was again approached about referral to a transplant center for CAR T vs clinical trial participation. Due to personal issues, the patient decided to enroll in a clinical trial instead of accepting the referral. The study treated the patient with a CD20/CD3 bispecific antibody. The patient tolerated the therapy well and again obtained a remission.

Authors' perspective: In a situation in which both CAR T and bispecifics are available, both options can be considered. However, for most patients, bispecifics, once approved, are likely to play a bigger role in R/R FL given their better accessibility and AE profile compared to CAR T, especially if long-term follow-up indicates that the ORR and DOR of bispecifics are similar to CAR T. In respect to this case, our preference would be to treat the patient with a bispecific antibody unless other factors (distance from the center) precluded the use of this drug class.

Future therapies

Several combination studies are underway with the drugs discussed previously. A current phase 1/3 study is evaluating tazemetostat in combination with R2 in patients with 2L and beyond.[46] Other future treatments that might hold promise in ER FL include CD20/CD3 bispecific antibodies, as previously discussed. Bispecific antibodies function like CAR T in that the mechanism of action is through T-cell activation. Unlike CAR T, which requires apheresis, antigen receptor modification, and then infusion of the modified cells, bispecific antibodies are an "off-the-shelf" therapy that functions by engaging CD20 on the surface of the

Table 4. Outcomes for early-relapsing patients with T-cell-directed therapies

Drug	ORR (overall)	ORR (POD24)	CR (Overall)	CR (POD24)	PFS (Overall)	PFS (POD24)	OS
Axi-cel[44]	94%	92%	79%	N/A	64.8% at 18 mo	55.3% at 18 mo	87.4% at 18 mo
Tisa-cel[45]	86.2%	N/A	69.1%	59%	67% at 12 mo	N/A	N/A
Mosunetuzumab[49]	78.9%	83%	57.8%	55%	17.9 mo median	N/A	N/A
Mosun + Len[50]	92%	N/A	77%	N/A	N/A	N/A	N/A
Glofitamab[48]	81%	N/A	70%	58%	N/A	N/A	N/A
Glofit + O[48]	100%	N/A	73.7%	70%	N/A	N/A	N/A
Epcoritamab[47]	90%	N/A	50%		N/A	N/A	N/A

Len, lenalidomide; N/A, not available; O, observation.

malignant B cell while binding to the patient's native T cells to induce T-cell activation and expansion. Preliminary data indicate a high ORR without any major difference in outcomes for ER vs non-ER patients, as indicated in Table 4. Bispecific antibodies, additionally, have similar AEs compared to CAR T, but current data suggest the bispecifics have lower incidences of all AEs, including CRS and ICANS. Outcomes of patients with FL treated with several of the bispecifics as well as the currently approved CAR T products are illustrated in Table 4. While the initial studies were composed of R/R FL patients who had received 3 or more prior lines of therapy, future trials are looking at utilizing bispecific antibodies in earlier lines of therapy. Several of these studies are exploring the combination of bispecifics together with either chemotherapy or lenalidomide. The results of these studies could exponentially expand the number of FL patients treated with these agents and in turn could affect the sequencing of options for later lines of therapy for FL patients.[47-50] The CD19 monoclonal antibody tafasitamab is currently approved for 2L and beyond DLBCL in combination with lenalidomide. As a single agent, tafasitamab was evaluated in FL and showed limited clinical efficacy but a high disease-control rate (a high percentage of stable disease). It is currently being explored in a phase 3 study in FL in combination with R2 vs R2 alone, as well as in a phase 1 study with the selective PI3Ki parsaclisib.[51]

Conclusions

While we have made substantial gains in the treatment and management of patients with FL, those with ER disease remain a group still in need of improved treatments. This is due to the poor OS of this group compared to those who remain in remission for at least 24 months after treatment. No current standard approach exists for managing patients who relapse early after initial CIT. How we would manage those with R/R FL is outlined in Figure 1. From our perspective, the biggest issues that remain are the lack of a tool to identify these patients prior to their initial relapse, the lack of a method to identify the transformation

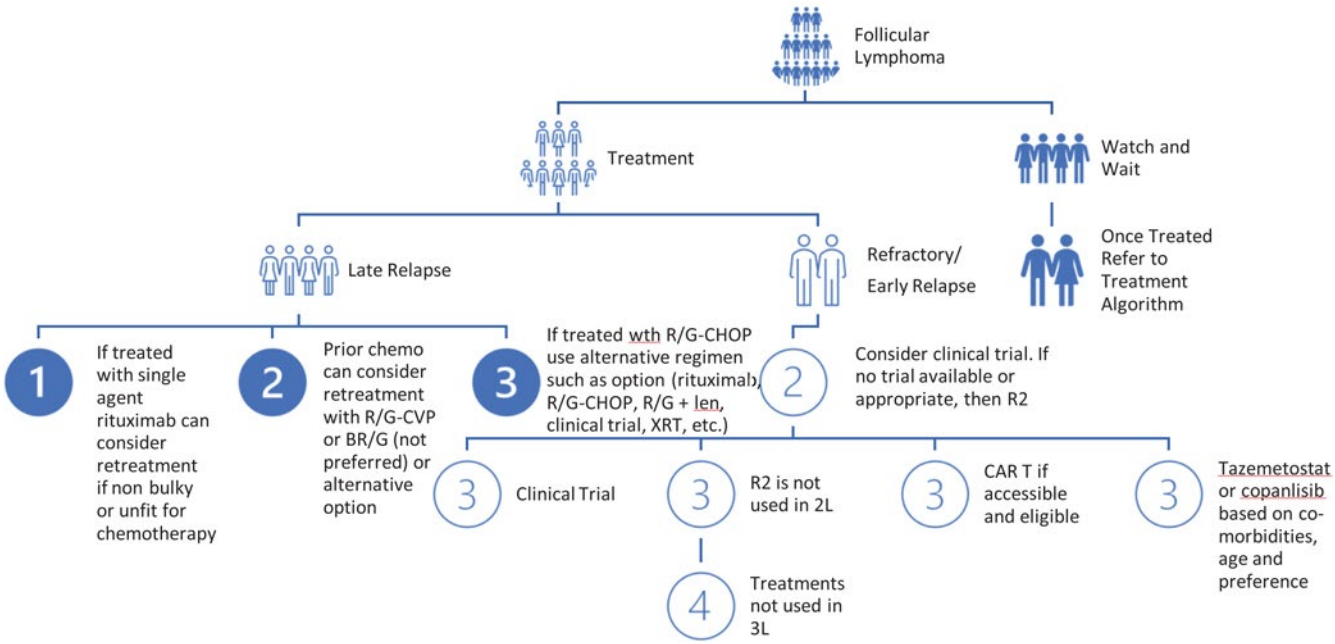

Figure 1. Our approach to patients with relapsed or refractory follicular lymphoma and how we sequence the current FDA-approved agents in the 2L and beyond, with a specific focus on the sequencing of agents in patients with early relapse or primary refractory disease. len, lenalidomide; XRT, radiation.

Table 5. Most common adverse events with new agents

Drug	AEs	SAEs	Drug discontinuation
Lenalidomide	Neutropenia, diarrhea, constipation, cough, fatigue, pyrexia, leukopenia, URI, anemia	Pneumonia, febrile neutropenia, neutropenia, pulmonary embolism, sepsis, pyrexia	14 due to AEs (neutropenia most common reason)
Copanlisib	Hyperglycemia, diarrhea, hypertension (transient), neutropenia	Pneumonia, pyrexia, hypergyclemia, pneumonitis	38 patients due to AEs (pneumonitis and neutropenia most common)
Tazemetostat	Nausea, diarrhea, alopecia, cough, asthenia, fatigue, URI, bronchitis	Neutropenia, pancytopenia, transient global amnesia, arrhythmia, myelodysplastic syndrome	8 patients due to AEs no common AE noted
Axi-cel	CRS, pyrexia, hypotension, headache, fatigue, nausea, anemia, ICANS, neutropenia, sinus tachycardia, tremor, chills, vomiting, diarrhea, anorexia, hypoxia, confused state, cough, encephalopathy, dizziness	Pyrexia, encephalopathy, pneumonia, confused state, hypotension, hypoxia, somnolence, febrile neutropenia aphasia, embolism, headache, neutropenia, urinary tract infection, agitation, aspartate aminotransferase increased	N/A
Tisa-cel	CRS, neutropenia, anemia, leukopenia, thrombocytopenia, neutropenia, febrile neutropenia, ICANS, headache, dizziness, diarrhea, infections, constipation, nausea, vomiting	Neutropenia, leukopenia, anemia, febrile neutropenia, thrombocytopenia, GI disorders	N/A

GI, gastrointestinal; N/A, not available; SAE, serious adverse event; URI, upper respiratory infection.

to DLBCL in a fair number of these patients at relapse, and the lack of an optimal 2L regimen. The clinical study 1608, a randomized phase 2 trial in ER R/R FL, is attempting to address the latter issue. Unfortunately, this study has had enrollment issues potentially related to the high number of transformation events in this patient population and, more recently, to the withdrawal of the PI3K inhibitors from the market, as 1 of the arms utilized umbralisib. While not specifically addressing this question, currently over 70 clinical studies are active and enrolling patients with R/R FL.

For those not treated in clinical studies, we discussed several options that have demonstrated promising outcomes and, for the most part, manageable toxicities. We have summarized in Table 5 the most common AEs of the various agents discussed here. Most of these drugs have demonstrated efficacy and response durations that appear agnostic to the negative impact of an ER. One of the most promising novel agents is lenalidomide, which, given its method of operation, has the potential to combine effectively with other immunotherapeutic agents in addition to its known synergy with rituximab and obinutuzumab. Additionally, copanlisib and tazemetostat remain potential options for patients in the 3L and beyond setting. Although still available, ASCT or MSD SCT is not likely to be utilized due to questionable efficacy (ASCT) or high toxicity (MSD/MUD). CAR T is an option for those who can wait for the manufacturing and have access to an appropriate treatment center, but without an improvement in toxicity, this therapy is likely to be limited to 3L and beyond. Looking to the future, the bispecific antibodies are the next agents likely to significantly affect treatment for R/R FL, with the potential to combine with most of the already approved agents. As we look to take the next step to bridge the gap between those with ER disease and those without, 2 key barriers remain: (1) early identification of at-risk patients prior to treatment initiation and (2) determination of the best salvage therapy and, if possible, a better frontline therapy to prevent these patients from suffering an early relapse of their disease.

Conflict-of-interest disclosure

Radhika Takiar: no competing financial interests to declare.
Yasmin Karimi: no competing financial interests to declare.
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Off-label drug use

Radhika Takiar: nothing to disclose.
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Correspondence

Tycel J. Phillips, City of Hope National Medical Center, 1500 E Duarte Road, Duarte, CA 91010; e-mail: tphillips@coh.org.

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