Sequencing of therapies in relapsed follicular lymphoma

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Follicular lymphoma (FL) is an incurable but treatable disease with vast treatment options. Despite the abundance of efficacious treatment modalities, there is no universally agreed upon standard approach to treatment, particularly in the relapsed/refractory setting. There is an increasing need for more robust and clinically available tools to risk-stratify patients and identify those likely to experience early relapse, which is currently recognized as the unmet need in FL. Additionally, the use of gene-expression profiling and next-generation sequencing techniques in recent years has led to a wealth of knowledge regarding the molecular drivers of lymphomagenesis. However, much of this knowledge is not currently available in the clinic to inform treatment decisions. Future studies are needed to generate clinically relevant predictive models adept at incorporating patient-specific and molecular features to inform management strategies along the entire disease continuum as treatment decisions should not be made in a vacuum with a one-size-fits-all approach. Sequencing of therapy in the management of relapsed FL should involve personalized decision-making for care plans that balance patient characteristics, preferences, and comorbidities with treatment-related factors such as efficacy, toxicity profile, and mechanisms of action to achieve a durable, quality remission.

Learning Objectives

- Identify high-risk FL patients to inform management strategies in the relapsed setting
- Examine the current treatment landscape in the relapsed setting to inform treatment selection

Introduction

Despite the prolonged natural history of follicular lymphoma (FL), prognostic indices such as the Follicular Lymphoma International Prognostic Index (FLIPI) are often applied at initial presentation and are generally not reassessed over the lifetime of patients.[1] Even with modern attempts to incorporate the genetics of FL into risk stratification, the M7-FLIPI can improve stratification of high-risk patients treated with frontline chemoimmunotherapy and identify approximately one-half of those with high-risk FLIPI who are likely to have good outcomes. In the relapsed setting where therapeutic strategies are even more vast, there is a paucity of risk-stratifying tools to inform treatment decisions. In addition, biomarkers to predict treatment response are highly desirable yet deficient. The best current surrogate markers for risk-stratifying patients in the relapsed setting are clinical features such as depth and duration of response following frontline chemoimmunotherapy. We highlight the available data and challenges in identifying the most effective strategies for sequencing therapy in FL.

Identifying patients at highest risk

With a disease characterized by a median overall survival (OS) approaching 2 decades, the most important strategy in achieving desirable outcomes is to identify patients with favorable-risk disease who may be candidates for less intensive, less toxic therapies. Similarly, efforts should be made to identify poor-risk features, as patients with these features face shortened survival; tailoring and/or intensifying therapy even if associated with higher toxicity is justifiable to alter the natural history of their disease course. FLIPI is the most widely used clinical prognostic index at diagnosis, risk-stratifying patients according to age, stage, hemoglobin, lactate dehydrogenase, and number of nodal sites; the index identifies approximately one-third of patients at risk for poor outcomes.[1] FLIPI-2 explored prognostic indices in the rituximab era and incorporated serum β2 microglobulin, bone marrow involvement, and tumor bulk (>6 cm); it does not require determination of the number of nodal sites, which improved the prognostic accuracy but has been less widely adopted.[2,3] Both FLIPI and FLIPI-2 were validated using the prospective PRIMA trial, and a simpler prognostic tool was derived based on bone marrow involvement and β2 microglobulin, predicting progression-free survival (PFS) for patients treated with frontline chemoimmunotherapy.[4] The M7-FLIPI, possibly the most novel in the modern era but less clinically applicable, is a clinicogenetic risk model that included the mutation status of 7 genes (*EZH2*, *ARID1A*, *MEF2B*, *EP300*, *FOXO1*, *CREBBP*, and *CARD11*), the FLIPI score, and Eastern Cooperative Oncology

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Group (ECOG) performance status, improving prognostication for patients receiving frontline chemoimmunotherapy; the M7-FLIPI identified a subset at highest risk for treatment failure.[5] Although these tools help identify patients who are at risk for inferior outcomes and identify the unmet need in regards to drug development, they are still mostly restricted to data interpretation across prospective studies and fail to inform treatment selection.

Despite the indolent nature of FL characterized by high response rates and robust remissions, relapse is inevitable for most patients in the form of recurrence or progression of FL. Histological transformation or evolution to a more aggressive lymphoma subtype (diffuse large B-cell lymphoma) occurs in ~2% to 3% of patients per year and is associated with poor outcomes.[6,7] Often feared as a turning point in the natural history of the disease, a potentially catastrophic event, not all patients with FL will transform. Identification of transformed lymphoma is critical to appropriate management and histologic confirmation is recommended for those with worrisome clinical features such as sudden increase in lactate dehydrogenase, rapid discordant nodal growth, new B symptoms, or hypercalcemia. Histologic grade (grade 3) and high-risk FLIPI score at diagnosis have been reported to predict the risk of histologic transformation.[8] Clinical suspicion and tissue sampling should be used when aggressive clinical features such as early progression or refractory disease occur.

Progressed and transformed FL appear to exhibit different clonal dynamics driven by distinct evolutionary mechanisms.[9] As opposed to progressive FL in which linear evolution leads to an expansion of a major diagnostic clone, transformed lymphoma is characterized by divergent evolution with emergence of an unrelated subclone that is either undetectable at diagnosis or at a low frequency. The analysis of circulating tumor DNA may afford the opportunity to capture alteration in the mutation burden over the course of the disease, identify early poor-risk events, and address spatial heterogeneity complicating tissue sampling. Tools that allow us to capture the evolving biology of relapsed FL may impact treatment decisions and management in the future. Although treatments are rapidly evolving, transformation still conveys a poor prognosis and should be considered when following patients with FL longitudinally as management strategies can be divergent from the approach to relapsed FL.

The depth and duration of response to frontline chemoimmunotherapy are important surrogate prognostic indices in relapsed FL and inform subsequent management strategies. Postinduction positron emission tomography (PET) imaging has correlated with outcomes. End-of-induction PET imaging across prospective studies confirmed a strong association with improved PFS and OS if patients achieved a PET^- status at the end of induction.[10] PET status was independent of FLIPI, FLIPI-2, and computed tomography–based response assessments in predicting survival. Therefore, a patient with a positive end of induction PET may be much more suitable for maintenance therapy or consolidation therapy than a patient with a negative PET given the risk for inferior outcomes.

Time to relapse or progression following initial chemoimmunotherapy has been a robust predictor of survival in FL. Randomized studies involving chemoimmunotherapy have consistently shown that ~20% of FL patients experience early progression of disease.[11-13] Consistent with these trials, an analysis of data from the National LymphoCare study in the United States involving patients with FL treated with first-line R-chemotherapy showed that 19% relapsed within 2 years.[14] Progression of disease within 24 months (POD24) of frontline chemoimmunotherapy is associated with poor 5-year survival rates (34%-50%), far inferior to the 90% 5-year survival rate of those without an early progression event. In addition, early progression of FL (POD24) has been validated as a robust end point associated with OS; the pretreatment M7-FLIPI has been shown to predict POD24 and OS.[15] Given the marked inferior prognosis associated with early relapse after frontline chemoimmunotherapy, this poor-risk group should be enriched on prospective trials to inform the preferred treatment approach for these patients. Early relapse is thus an emerging and important prognostic factor that may help risk-stratify high-risk patients in a good prognosis disease.

The limitation of existing prognostic models is the failure to predict FL patients at risk for early relapse. New models that predict poor outcomes prior to treatment failure are needed to personalize treatment approaches. Gene-expression signatures performed on pretreatment samples in the prerituximab era predicted survival among patients with FL, which correlated with molecular features on the nonmalignant tumor-infiltrating cells.[16] In the rituximab era, gene-expression profiling data were analyzed to build and validate a model to predict risk of progression at 2 years among patients treated with frontline chemoimmunotherapy.[17] The 23-gene predictive score identified 2 groups of patients with FL with markedly distinct outcomes when treated with chemoimmunotherapy. In multivariate analyses, the model was able to predict PFS independent of rituximab maintenance and FLIPI score. Being able to identify a low-risk group could allow for shorter duration and less toxic therapy whereas high-risk patients can be identified and referred for clinical trials to access novel therapy.

Management of relapsed FL

The preferred approach to high-risk patients is unknown. Phase 2 studies in the prerituximab era suggested that high-dose therapy (HDT) followed by autologous stem cell transplant (ASCT) is associated with robust remissions. However, the best results were achieved when the treatment was administered earlier in the course of the disease and in the setting of remission.[18-22] Concerns regarding mortality from secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) curbed enthusiasm surrounding myeloablative therapy in FL. HDT/ASCT in the modern era reported rates of secondary MDS/AML of 12.4%, though approximately one-half of patients achieved robust remissions when treated early in the course of the disease. The risk is high, but the reward can also be favorable if performed in second remission. HDT/ASCT should be restricted to the highest-risk patients, those who experience early relapse following frontline chemoimmunotherapy.

Radioimmunotherapy, radiation-emitting radionuclide combined with an antibody targeting CD20, is an effective therapy in FL as consolidation following frontline chemotherapy or in the relapsed setting.[23-25] Myelosuppression is the primary toxicity and secondary MDS and AML rates appear similar to those observed with chemotherapy. The most favorable outcomes are observed in patients with low bulk disease, fewer prior therapies and rituximab sensitivity (Table 1). With a single administration, this may be an attractive approach for a select group of patients.

Targeted therapy for relapsed FL

Obinutuzumab is US Food and Drug Administration (FDA)-approved for relapsed patients with FL based on the GADOLIN study that compared obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance to bendamustine alone in patients with rituximab-refractory indolent lymphoma. With

Table 1. Outcomes for relapsed follicular lymphoma

Therapy	Target	N	CR, %	ORR, %	mDOR, mo	mPFS, mo
Rituximab[32]	CD20	70	16	56	12	—
Obinutuzumab + BR[26]	CD20 + chemo	164	16	79	NR	25.3
^{90}Y ibritumomab tiuxetan[25]	CD20/RIT	73	30	80	14.2	—
Idelalisib[27]	PI3Kδ	72	6	57	12.5	11
Copanlisib[28]	PI3Kαδ	102	14	59	13	11.2
Lenalidomide + rituximab[30]	IMID/ CD20	128	30	66	NR	1 y, 70%
Ibrutinib[33]	BTK	40	12.5	37.5	13.9	14
Tazemetostat[31]	EZH2	67	6	39	—	—
CAR T[34]	CD19	14	71	79	—	NR

—, data unavailable; BR, bendamustine and rituximab; BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; chemo, chemotherapy; CR, complete response; EZH2, enhancer of zeste homolog 2; IMID, immunomodulatory drug; mDOR, median duration of response; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate; PI3K, phosphatidylinositol 3-kinase; RIT, radioimmunotherapy.

a median PFS of 25.8 months vs 14.1 months, the obinutuzumab-containing arm was superior to chemotherapy alone.[26] Neutropenia was one of the most common grade 3 or higher adverse events observed at 27.5%. Obinutuzumab in combination with bendamustine in rituximab-refractory patients was far superior to chemotherapy alone and resulted in an improvement in OS. As many patients will receive frontline bendamustine in combination with anti-CD20 therapy, how to interpret or integrate the GADOLIN data in the modern era is less clear.

Targeting the B-cell receptor signaling pathway has been an effective approach for relapsed/refractory FL in the third-line or later setting. There are 2 FDA-approved phosphatidylinositol-3-kinase (PI3K) inhibitors for the treatment of patients with relapsed/refractory FL who have failed at least 2 prior lines of therapy: idelalisib (PI3Kδ inhibitor) and copanlisib (PI3Kα and δ inhibitor). Both have similar efficacy profiles with nearly 60% of patients achieving an objective response with a median PFS of ~11 months.[27,28] The PI3Kδ inhibitor, idelalisib, was FDA-approved based on data from a study involving FL patients who were "double refractory" to anti-CD20 antibodies and alkylating agents and demonstrated an overall response rate of 54% and a median duration of response of 11 months.[27] More recently, copanlisib, an IV PI3Kα and δ inhibitor was approved based on similar efficacy data.[28] There appears to be a differentiated safety profile, with transient hyperglycemia and hypertension being some of the most frequent treatment-emergent adverse events associated with copanlisib, with lower rates of transaminitis and colitis than observed with idelalisib. With 2 available agents, selection can be personalized based on the anticipated safety profile. For instance, copanlisib may not be the preferred option for a patient with uncontrolled hypertension or diabetes mellitus.

Early relapse has been a reproducible poor prognostic feature; however, it is unclear whether this time to event is a surrogate marker of aggressive biology or a clinical feature of chemorefractoriness that may be overcome with targeted therapy. Limited data exist regarding the outcomes associated with the sequencing of therapy in FL, which remains important because most patients relapse and require sequential treatment. Moreover, no completed prospective study exists regarding the impact of sequential therapies among the most vulnerable FL patients who require a second treatment within 2 years of initial therapy. A retrospective post hoc analysis in a subgroup of patients with relapsed FL in the phase 2 study of idelalisib in relapsed indolent lymphoma was performed to examine whether idelalisib could overcome the poor-risk feature of early relapse following frontline chemoimmunotherapy.[29] The efficacy and safety profile of idelalisib in this poor-risk population compared favorably to the general study population. This hints that targeted therapy may be a reasonable option for poor-risk patients as well and can be explored in the third-line setting with the FDA-approved agents.

Lenalidomide in combination with rituximab in relapsed FL is also being explored for patients with relapsed FL. The phase 3 AUGMENT trial (NCT01938001) examining the efficacy of lenalidomide and rituximab (R^2) in comparison with rituximab monotherapy in relapsed/refractory FL and marginal zone lymphoma has met the primary end point of superior PFS with R^2. The phase 3 MAGNIFY trial (NCT01996865) examines 12 cycles of R^2 followed by maintenance of R^2 vs rituximab monotherapy. Preliminary data have reported promising efficacy, with a 1-year PFS of: 70%; 65% for double refractory (refractory to CD20 and alkylating therapy); and 49% for early relapse patients.[30] The ongoing AUGMENT study will address whether lenalidomide adds additional efficacy when combined with rituximab in comparison with rituximab monotherapy in relapsed/refractory FL; at this time, R^2 appears to be a promising option in the relapsed setting.

Intergroup trial S1608 (NCT03269669) is a prospective, randomized phase 2 study examining targeted approaches vs chemotherapy in patients with FL who experienced early treatment failure following frontline chemoimmunotherapy. The study has 3 arms: obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); obinutuzumab in combination with lenalidomide; and obinutuzumab in combination with umbralisib (TGR1202, PI3Kδ inhibitor). Patients can move on to autologous or allogeneic hematopoietic cell transplantation at the discretion of the investigator after ~6 months of therapy. This is an important prospective study that may identify the preferred management strategy for high-risk FL patients and should be pursued for any patient experiencing early relapse.

Additional novel agents are under investigation for the management of relapsed/refractory FL including tazemetostat, an enhancer of zeste homolog 2 (EZH2) inhibitor. EZH2 has an essential role in the pathogenesis of FL and recurrent gain-of-function mutations have been described in ~25% of FL patients. Early phase studies exploring the activity and safety of tazemetostat appear promising in relapsed FL.[31] In addition, adoptive cellular therapy in the form of chimeric antigen receptor (CAR) T may prove to be an effective strategy for chemorefractory disease. Two CAR T-cell therapies are currently FDA approved for the treatment of transformed lymphoma after 2 lines of therapy. Clinical trials are under way to examine the efficacy and safety in high-risk relapsed FL. Balancing the risk of disease and toxicity profile warrants further exploration particularly in high-risk patients. Future studies examining predictive factors for earlier transition to next-line treatment will provide clinicians with more specific information to use in the decision-making process, and will be particularly valuable for patients with high-risk FL.

Conclusions

A personalized approach to sequencing therapy in FL is warranted to minimize acute and late toxicity and achieve durable, quality remissions given the anticipated prolonged natural history of this disease. Improved risk stratification and predictive biomarkers are

highly desired to inform treatment decisions. This could then allow for dynamic profiling of tumors at progression and inform the next treatment selection accounting for prior therapy and outcomes. Until this is realized, applying known clinical prognostic models to identify those at both ends of the spectrum, low and high risk, will then inform therapy selection based on the goal, achieving a durable remission to extend survival among those facing poor prognosis or minimizing toxicity and the impact on quality of life among those anticipating favorable life expectancy.

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