Recent Developments in the Treatment of Follicular Lymphoma

BY RICHARD SIMONEAUX

Follicular lymphoma (FL) is one of the most common forms of indolent non-Hodgkin lymphoma (NHL). This disease is typically characterized by slow progression with relapses that may occur up to 2 decades after initial diagnosis. This disease, although being considered indolent, is typically manageable but not curable.

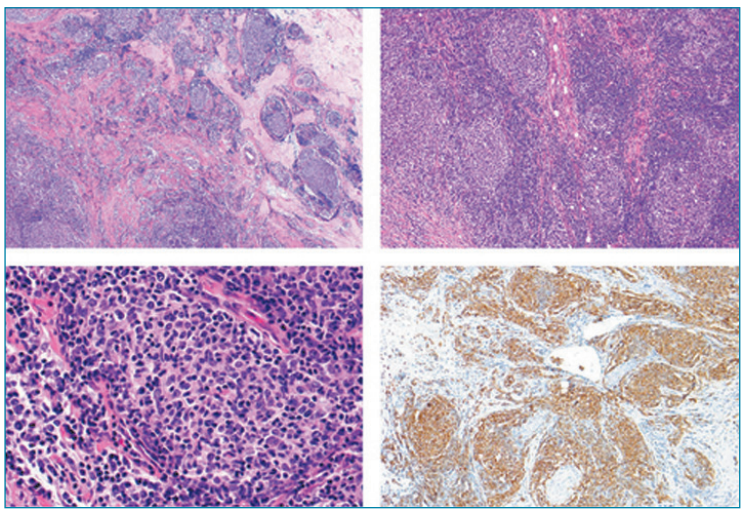
Patients who have FL and undergo disease progression less than 2 years post-diagnosis or whose disease is refractory to rituximab combinations or monotherapy typically experience shortened survival. As a result, there is a clear clinical need for novel therapies which can bolster the activity of treatments for this patient population.

Recently, *Oncology Times* had a discussion with Nathan Fowler, MD, Associate Professor in the Department of Lymphoma/Myeloma at The University of Texas MD Anderson Cancer Center, regarding current developments within the field of FL treatment. "Currently, it is an exciting time to be treating FL patients, as there are a number of novel monotherapies and combinations that are being evaluated in this population. In addition, for the first time, a molecular aberration has been effectively targeted therapeutically for FL," he noted.

FL is divided into three different grades. "In clinical practice, grades 1 and 2 disease are treated similarly, while grade 3 FL is treated more vigorously, as it is more aggressive," Fowler explained. "Grade 3 FL is further subdivided into two separate disease states, 3a and 3b. Grade 3b tends to be more aggressive, while grade 3a can behave in a manner that is either indolent or aggressive, depending on the presence of clinical factors such as lactate dehydrogenase levels. Many current clinical trials involving FL specifically exclude those patients with grade 3b, as there is growing evidence that it may be a distinct disease state," he commented.

Lenalidomide + Rituximab

In the RELEVANCE international phase III superiority trial (NCT01476787 and NCT01650701), the use of lenalidomide plus rituximab (also referred to as the R^2 regimen) was compared with rituximab plus investigator's choice of chemotherapy in previously untreated FL patients with grade 1, 2, or 3a disease (*N Engl J Med* 2018;379:934-947). The following regimens served as comparators for the experimental arm of lenalidomide plus rituximab: rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP); rituximab + cyclophosphamide + vincristine + prednisone (R-CVP); rituximab + bendamustine (R-B). After finishing their respective courses, all patients received maintenance rituximab monotherapy. The primary endpoints for this study were progression-free survival (PFS) and confirmed or unconfirmed complete response (CR) at 120 weeks.



Between November 2011 and December 2014, 1,030 patients were randomized to either rituximab plus lenalidomide (n=513) or rituximab plus chemotherapy (n=517).

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For the patients in the rituximab plus chemotherapy group, the breakdown by regimen was as follows: R-CHOP—372; R-B—117; R-CVP—28. After a median follow-up time of 37.9 months, the independent review committee (IRC)-assessed PFS at 3 years was 77 percent (95% CI: 72-80%) for the rituximab plus lenalidomide group and 78 percent (95% CI: 74-82%) for the rituximab plus chemotherapy group, affording a hazard ratio (HR) of 1.10 (95% CI: 0.85-1.43).

For the study's other primary endpoint, confirmed or unconfirmed CR, the values for the rituximab plus lenalidomide and rituximab plus chemotherapy groups were 48 percent (95% CI: 44-53%) and 53 percent (95% CI: 49-57%), respectively.

"Although this study was designed to show superiority for rituximab plus lenalidomide, the results were very similar for both study groups," Fowler noted. "Despite the fact that superiority was not shown for the R^2 regimen, the results were still significant, as this was the first time that chemo-like results were obtained for this patient population without many of the adverse effects associated with chemotherapy."

The phase III AUGMENT study (NCT01938001) evaluated the use of rituximab plus lenalidomide (R^2) versus rituximab plus placebo in previously treated patients with relapsed or refractory indolent lymphoma, including FL and mantle zone lymphoma (*J Clin Oncol* 2019; doi:10.1200/JCO.19.00010). In this study, patients were randomized in a 1:1 manner to either lenalidomide plus rituximab (n=178) or placebo plus rituximab (n=180). As with the RELEVANCE study, patients with grade 3b or transformed FL were excluded from participation. The number of patients having FL were evenly divided between the two study groups: lenalidomide plus rituximab (147) and placebo plus rituximab (148). The study's primary endpoint was IRC-assessed PFS.

The median IRC-assessed PFS was 39.4 months (95% CI: 22.9 months-not reached) for the lenalidomide plus rituximab group and 14.1 months (95% CI: 11.4-16.7 months) for the placebo plus rituximab group, providing an HR of 0.46 (95% CI: 0.34-0.62; $p< 0.001$), favoring the R^2 regimen. Interestingly, subgroup analysis showed that there was no advantage for those patients having marginal zone lymphoma (MZL), as an unstratified HR of 1.00 (95% CI: 0.47-2.13) was obtained for PFS analyses for this subset.

"There was a clear signal for the R^2 regimen relative to the placebo plus rituximab therapy for those patients with FL," Fowler noted. "Although, higher incidence of neutropenia was noted with the R^2 regimen, this was not a surprise, as this trend had been noted in other trials with lenalidomide. This adverse effect was effectively managed and did not diminish in any way the strength of the efficacy data."

PI3K Inhibitor Therapy

The DYNAMO open-label, single-arm, phase II clinical trial (NCT01882803) assessed the safety and efficacy of the PI3K inhibitor duvelisib in indolent NHL patients with disease that was refractory to rituximab (monotherapy or in combination) and chemotherapy or radioimmunotherapy (*J Clin Oncol* 2019;37(11):912-922). Patients with FL (n=83), small lymphocytic lymphoma (SLL) (n=28), or marginal zone B-cell lymphoma (n=18) were included in this study. The primary endpoint of this study was IRC-assessed overall response rate (ORR), defined as the patients having CR plus those having a partial response (PR).

There were a total of 129 patients included in this study and, for this population, the ORR was 47.3 percent (95% CI: 38.4-56.3%). When separated by disease type, the following ORR values were obtained: FL–42.2

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percent (95% CI: 31.4-53.5%); SLL–67.9 percent (95% CI: 47.6-84.1%); and marginal zone B-cell lymphoma–38.9 percent (95% CI: 17.3-64.3%).

"The results obtained in this study were quite compelling, especially when one considers the heavily pretreated nature of the patients included," Fowler said. "The toxicities were fairly standard for this class of compounds, likely resulting from T-cell dysregulation.

"Several studies involving PI3K inhibitors are ongoing [to explore] dose interruption or modification to minimize the T-cell dysregulation that occurs with this type of therapy," Fowler commented. "Generally speaking, this is a great class of compounds with real promise in indolent lymphoma."

In September 2018, the FDA granted accelerated approval to duvelisib for the treatment of FL patients who had two or more previous systemic therapies. In that same announcement, duvelisib was also approved for the treatment of patients with chronic lymphocytic leukemia or SLL who had two or more prior therapies.

Anti-CD47 Antibody + Rituximab

The surface-bound protein CD47, which is overexpressed on most cancer cells, is an antiphagocytic signal (also referred to as the "do not eat me" signal) that allows those tumor cells to evade the immune system's macrophages and other phagocytes. CD47 overexpression has been shown to be an independent predictor for poor prognosis in patients having various malignancies, including lymphoma (*Cell* 2010;142:699-713).

Mechanistically, anti-CD47 antibodies are thought to induce phagocytosis of malignant cells by blocking the interaction of CD47 and its ligand, SIRPα. In addition to macrophages, anti-CD47 antibodies may also assist the immune system by inducing an antitumor T-cell response via the cross-presentation of tumor antigens to T cells by phagocytes. Hu5F9-G4 is a CD47-blocking humanized monoclonal antibody being

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Learning Objectives for This Month's CME Activity:

After participating in this CME/CNE activity, readers should be better able to: 1. Describe novel monotherapies and combination therapies under evaluation for patients with follicular lymphoma (FL).

Disclosure: The author(s), faculty, staff, and planners, including spouses/partners (if any), in any position to control the content of this activity have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

A Q&A on Follicular Lymphoma Transformation

BRIAN K. LINK, MD

Although follicular lymphoma (FL) is typically an indolent disease with a course of progression that can last for decades, there are some patients who have disease that undergoes transformation to a more aggressive malignancy. To discuss this important topic, *Oncology Times* interviewed FL expert Brian K. Link, MD, Professor of Internal Medicine-Hematology, Oncology and Blood and Marrow Transplantation at the University of Iowa.

How frequently do FL patients undergo transformation?

Several recent international studies have shown that 20-25 percent of patients with FL develop clinically evident transformation to a more aggressive lymphoma within a decade of diagnosis. The exact rates fluctuate amongst the reports, which all have slightly different patient selections and definitions for transformation. Beyond a decade, the data are somewhat less reliable but suggest an ongoing risk of about 1-3 percent per year. Clinically evident transformation is a profound event for patients with FL because, although the prognosis post-transformation is not as dire as it once was, recent research highlights that, of all FL patient deaths attributable to lymphoma, nearly half are following a clinically evident transformation event (*J Clin Oncol* 2019;37(2):144-152).

What are some of the aggressive malignancies to which FL can be transformed?

The overwhelming majority of transformation events result in a diffuse large B-cell lymphoma diagnosis or the recently defined entity high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements. FL patients will rarely develop Burkitt lymphoma or acute lymphoblastic leukemia/lymphoma.

Why do some FL patients undergo transformation while some don't?

We are best served if we abandon the traditional paradigm that transformation is a distinct dichotomous event and consider clinical transformation as more of an emergence. Clinical FL emerges from a proliferation of clonal lymphocytes composed of innumerable genetically distinct subclones. At any given time, these diverse subclones are under a variety of competitive or selective pressures to survive, expand, or even die out. For unclear reasons, a subclone with an aggressive lymphoma phenotype can rapidly attain clonal dominance in the transformed biopsy sample. The preponderance of new research reports show that key genetic drivers of transformed behavior already existed in subclones at the time of initial FL diagnosis.

Are there any ways to predict which FL patients will undergo transformation?

A multitude of retrospective analyses involving FL patients with and without transformation have, with limited reproducibility, attempted to identify clinical, histologic, genetic, or metabolomic factors at time of diagnosis that may predict subsequent transformation. Common clinical features at the time of FL diagnosis associated with higher risk of transformation include elevated serum lactate dehydrogenase levels, a high-risk FLIPI score, bulky/extranodal disease, and B symptoms. Some but not all studies find grade 3 histology has the highest risk of transformation as has the expression of the interferon regulatory factor 4 protein. Efforts to identify genetic biomarkers predictive of clinical transformation are very preliminary, with early candidates including somatic gene mutations in *BCL6*, *BCL2*, *MYC*, *MDM2*, or *CDKN2A*.

Are there any current strategies to circumvent FL transformation?

Several studies seek the answer to this question. Most are retrospective analyses of either prospectively or retrospectively assembled cohorts, making unmeasured variables hard to account for. The first obvious question is whether systemic therapy at time of FL diagnosis "prevents" or is at least associated with reduced risk of subsequent clinically evident transformation. Two large observational studies included over 3,200 newly diagnosed FL patients after the availability of rituximab therapy. Both studies showed statistically reduced rates of transformation over time in patients receiving initial systemic therapy compared to those who deferred that therapy, with HRs of approximately 0.6 after risk factor adjustment. OT

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evaluated in a phase Ib clinical trial (NCT02953509) in combination with rituximab in patients with NHL (*N Engl J Med* 2018;379:1711-1721).

This study included 22 patients total that had either diffuse large B-cell lymphoma (DLBCL, n=15) or FL (n=7). The majority of patients had rituximab-refractory disease (95%), while receiving a median of four prior therapies (range: 2-10). The trial contained three dose-escalation cohorts, with a 3+3 design in which a minimum of three patients per cohort were enrolled at every dose level. The safety profile at one level then guided the dose escalation in the subsequent cohort. Primary endpoints included safety evaluation and determination of the recommended phase II dose range for Hu5F9-G4 in combination with rituximab, while secondary objectives included efficacy (as measured by response), pharmacokinetics, and immunogenicity profiles for this antibody.

AEs were largely grade 1 or 2, with the most frequently observed being anemia and infusion-related reactions. The anemia, which is an expected effect, was managed by adopting a strategy of prime and maintenance antibody dosing. The dosage selected for phase II studies was 30 mg/kg Hu5F9-G4; at this level, approximately 100 percent CD47 receptor occupancy was noted for circulating white and red blood cells. Regarding efficacy, the ORR for all patients in this study was 50 percent (CR–36%; PR–14%), and for the subset of patients having FL, the ORR was 71 percent (CR–43%; PR–29%).

"These data were particularly promising, given the rituximab-refractory disease which most participants in this study had," noted Fowler. Further investigation is ongoing in the phase II portion of this trial (NCT02953509), where DLBCL, FL, and mantle zone lymphoma patients will receive Hu5F9-G4 plus rituximab.

EZH2 Inhibitor Therapy

Activating mutations to enhancer of zeste homolog 2 (EZH2) can lead to abnormal epigenetic modification (i.e., histone methylation), resulting in oncogenic transformation and disease which is dependent on EZH2 activity. Tazemetostat, a first-in-class selective inhibitor of EZH2, was evaluated for safety, clinical activity, and pharmacokinetics in a first-in-human phase I clinical trial (NCT01897571) (*Lancet Oncol* 2018;19:649-659).

From June 2013 to September 2016, a total of 64 patients were enrolled; of these participants, 43 had advanced solid tumors, while 21 had B-cell NHL (DLBCL-13; FL-7; MZL-1). This was a standard 3 + 3 dose-escalation study followed by expansion of the two highest-dosed cohorts below the maximum tolerated dose. The study's primary endpoint was determination of the maximum tolerated dose or recommended phase II dose for tazemetostat monotherapy (oral BID), based on investigator-reported dose-limiting toxicities, laboratory values, and other safety or pharmacokinetic values.

The most common treatment-related AEs were asthenia (33%), nausea (20%), anemia (14%), muscle spasms (14%), vomiting (9%), and anorexia (6%). These AEs were usually mild, typically grade 1 or 2 in severity.

The recommended phase II dose determined in this study was 800 mg twice daily. This figure was derived using safety and tolerability, on-target pharmacodynamics, pharmacokinetics, and clinical efficacy data consisting of CRs, PRs, or prolonged stable disease.

As of the data cutoff date (Nov. 11, 2016), the ORR was 38 percent for the study's B-cell NHL patients (95% CI: 18.1-61.6%). This figure included three ^{18}F-FDG PET-confirmed CRs (DLBCL–1 and 2–FL), and five PRs (DLBCL–3, FL–1, and MZL–1). One patient having a tumor with a *Y646H* mutation had a durable PR before disease progression after 16 months in the study. This was consistent with preclinical data that showed lymphomas having *EZH2*-activating mutations are particularly sensitive to this class of inhibitor.

"These results are especially notable, as this marks the first time that a targetable mutation has been utilized for therapy in FL," Fowler stated. "Patients having *EZH2*-activating mutations account for roughly 15-20 percent of those having FL. For this patient subset, EZH2 inhibition appears to be a very effective therapeutic strategy, as ORRs of up to 90 percent have been obtained for tazemetostat."

Future of the Research

"This is a very exciting time to be treating patients with FL, as there are several new treatment options for managing this disease for patients who undergo relapse," Fowler noted. "In the next few years, I expect there to be an expanded effort to do sequencing analyses on untreated FL patients in order to gain better insight into subsets which may be at higher risk for transformation or developing resistant disease.

"I also expect there to be increased dose modification with the existing therapies, in order to balance efficacy with mitigation of treatment-related AEs," he stated. "Most of the early studies used fairly simple dosing with treatment until progression to maximize efficacy signals; however, we may be able to provide similar benefit with shorter or less-intense schedules. I am also excited about new combination therapies that are emerging for treating this patient population." OT

Richard Simoneaux is a contributing writer.

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durvalumab alone as first-line treatment of mBC (https://clinicaltrials.gov/ct2/show/NCT03459846).

Another phase II trial studies afatinib, a protein kinase inhibitor of HER2 and EGFR, after first-line chemotherapeutic failure (https://clinicaltrials.gov/ct2/show/NCT02122172). Afatinib is a drug used successfully as a treatment in non-small cell lung carcinoma.

Sapanisertib is an experimental drug that inhibits mTOR, which is needed for cell growth, proliferation, and survival (*Nat Rev Cancer* 2018;18:744-757). TSC1/2 negatively regulates mTOR and a phase II trial is recruiting patients with *TSC1/2* mutations, for which sapanisertib may be an interesting drug (https://clinicaltrials.gov/ct2/show/NCT03047213).

Cabozantinib is a fourth precision drug that is currently approved for kidney cancer but is now also investigated for mBC in conjunction with nivolumab (PD-1) and ipilimumab (CTLA-4). Cabozantinib blocks c-Met and VEGFR2 protein production, both involved in cell proliferation (https://clinicaltrials.gov/ct2/show/NCT03866382).

Finally, FGFR inhibition is an exciting topic of interest for the BC community, as *FGFR3* mutations (10%) or overexpression of FGFR3 (40%) are frequent events in MIBC (*Clin Cancer Res* 2018;24:1586-1593). Moreover, FGFR3-TACC3 fusions are also found in MIBC (1-3%) (*Oncotarget* 2017;8:16052-16074). Erdafinitib (FGFR inhibitor) showed a 42 percent CR in patients with chemo-refractory or chemo-ineligible FGFR-altered mBC. In fact, in April 2019, the FDA granted accelerated approval to erdafitinib for patients with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* or *FGFR2* genetic alterations that showed progression during or following platinum-containing chemotherapy. Further phase III studies will hopefully show beneficial long-term effects of erdafitinib. **Table 1** provides an overview of discussed promising novel treatments for locally advanced, unresectable or mBC.

Upcoming BC research will be defined by new biomarker-driven trials for BC patients. Well-designed illustrations of these trials are the NCI-MATCH, NCI-MPACT, and BISCAY trials (*Curr Probl Cancer* 2017;41(3):182-193, *J Clin Oncol* 2016;34:TPS4577-TPS4577). In these trials, biomarker analysis precedes and pre-selects actual patients and drugs before treatment commences and, therefore, these studies are excellent examples of precision medicine.

Many new precision drugs are imminent for BC. Some are very promising (erdafitinib), whilst others still need further validation. One new molecular therapy definitively gained momentum: PD-1/PD-L1 ICI. For ICIs, one of the future challenges is to develop biomarker-driven patient selection. Eventually, precision medicine will allow us to treat BC patients with the customized therapies they need. OT